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SACRO-ILIAC STRAIN.

By Wm. S. Baer, M. D.,

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Much has been written in recent years, particularly by orthopedic surgeons, concerning sacro-iliac strain. But the subject seems to me to deal with a class of cases which are constantly being seen by the general practitioner—a class of cases which is somewhat puzzling, and yet whose treatment is very simple. Risking triteness, I venture to bring it before you to-day.

We have all, I am sure, been rather wearied, and at times even annoyed—annoyed possibly because of our own ignorance—by patients who present themselves before us complaining of pain—a pain continuous and at times severe—in the small of the back or down the thigh. At times the pain is a simple ache, but at times of such severity that one can neither work nor sleep. We have called it rheumatism, sciatica, lumbago, pelvic disease, and other things, and most often it has defied our therapeutic efforts, as well as the wisdom of the gynecologist.

Many of these constant backaches—be they mild or severe—acute or chronic—are due simply to a strain or sprain of the sacro-iliac joint.

Just as we twist our foot and get a sprained ankle, so we wrench, from one cause or another, the ligaments holding together the sacrum and ilium, causing a strain or sprain of the sacro-iliac joint.

Anatomy and Physiology of the Sacro-Iliac Joint.

The term sacro-iliac synchondrosis is a misnomer. The more recent investigations of anatomists, obstetricians and orthopedists show that the sacro-iliac joint possesses all the true histological structures of a true joint; that the articulating surfaces of the sacrum and the ilium are covered by cartilage, and this in turn by a thin layer of synovial membrane. So it naturally follows that, being a joint, it must possess a definite amount of motion, although this motion is small in amount, owing to the configuration of the joint surfaces and to the strength and tightness of its ligamentous bindings. This motion has been definitely measured by anatomical observers in the laboratories, and by the obstetrician in his practice. The amount of motion varies under different conditions and is always greater at the time of parturition, when it plays an

important rôle in the mechanism of labor, increasing the superior and inferior straight diameter of the pelvis at different times during labor. The strain on the sacro-iliac joint is tremendous, carrying as it does the weight of the entire torso. When we take into consideration the angle at which the joint is placed and remember the load it has to carry, and that it is a true joint with a definite amount of motion, is it surprising that a strain of the sacro-iliac joint is so very common?

The sacrum may swing in one of two directions, either forward or backward, with the third sacral segment acting as the axis. So we may divide sacro-iliac strain into two classes: Class A, in which the sacrum in its superior border tilts backward. Class B, in which the sacrum in its superior border tilts forward, presenting to us a flat or a hollow back. These two types must be clearly differentiated, for they show an entirely different set of symptoms, are different in their etiology and must necessarily be treated in a totally different manner. Again, either one or both sacro-iliac joints may undergo strain that produces in the one-sided kind a lateral deviation of the spine, while in those cases in which both joints are involved, there is generally no lateral deviation, but simply an increase or diminution in the normal lumbar lordosis.

Etiology.

Class A, in which the sacrum tilts backward. This is the most important class, so far as the severity of the symptoms is concerned. In this class the etiological factors are numerous, and may be subdivided as follows:

1. *Strains Due to Childbirth.*—As has been stated, the normal amount of motion is increased during the mechanism of labor, so as to increase at different times the superior and inferior pelvic diameter. In many cases of difficult labor, the strain put upon these joints is beyond its normal physiological amount of motion, and the amount of motion therefore becomes pathological, resulting in the disability of the patient for a long period after her delivery. The strain in these cases may be either unilateral or bilateral.

2. *Traumatism (Direct).*—The strain of the sacro-iliac joint may be due to a direct blow. In my experience, several such cases have been due to cranking an automobile while in gear. The machine, startled from its inactivity, has pushed the patient's sacrum into some neighboring object. Many cases are due to direct violence, such as being struck over the sacrum by heavy timbers; others are due to falls directly upon the sacrum.

3. *Traumatism (Indirect).*—This constitutes by far the most frequent etiological factor. It is due to muscular strain, caused by the activity of the patient himself while performing some task greater than his muscles will stand, or by some sudden twist, when the muscles hold rigidly and hence throw too much strain upon the ligaments of the sacro-iliac joint. This is well exemplified in stevedores or others who pick up heavy loads while in a stooping position. Athletes, or pseudo-athletes, as golf players, often strain this joint in the swing of the body which follows a drive. Tennis players and tenpinists are subject to the same trouble. I can recall the case of a prominent physician who suffered an acute attack of sacro-iliac strain while shoving his boat from the shore with an oar. In fact, occupations that throw an excessive strain upon the quadratus lumborum and erector spinæ muscles, while the muscles of the legs are braced to hold the pelvis firm, will cause a giving away of the ligamentous structure binding the sacrum and the ilium, and thus produce a strain of the sacro-iliac joint.

4. *Static Influence.*—If for any reason one sacro-iliac joint is placed under greater strain than the other, the symptoms will often be referred to that joint. Such is the case when one leg is shorter than the other, as in cases of hip disease, coxa vara, or anterior poliomyelitis of one leg, etc.

5. *Congenital Malformation.*—Occasionally one finds that in the osseous formation of the spine the transverse process of the fifth lumbar vertebræ is fixed into the ilium and sacrum at the articulation; such a condition allows of no motion in the joint. An undue amount of motion necessary for the mechanics of the body is then thrown upon the other sacro-iliac joint, producing the usual symptoms of strain in that joint.

In Class B, when the sacrum is tilted forward, and there is in consequence a hollow back, other etiological factors are the rule.

1. *Static Influence.*—This is particularly the case in girls from 12 to 20 years of age, who have outgrown their muscular strength, and whose muscles lack the tone necessary to keep the body in an erect position.

2. *Neurological diseases,* as anterior poliomyelitis or progressive muscular atrophy, in which again the spinal muscles are involved, and one is no longer able to hold one's self erect.

3. *General visceroptosis,* when all the abdominal organs are markedly misplaced and have drifted from their normal position, even at times into the pelvis. This is particularly noticeable in women, whose continued pregnancies have caused a marked relaxation of the abdominal muscles, which has allowed the visceroptosis to occur. In fact, it might be stated that, as a rule, in Class A the majority of the patients are males, in Class B the women predominate.

4. *Intrapelvic tumors or misplacements*—myomata, sarcoma of the ovaries, or ovarian cysts, indeed, retro- or anteflexion of the uterus—all tend to a strain of the sacro-iliac joint, with an increase in the lumbar lordosis.

5. *Adiposity,* when the increase of abdominal fat drags on the lumbar spine and the strain is necessarily thrown on the sacro-iliac joints.

These are only a few of the factors causing strain of the joints under consideration.

Symptomatology.

The symptoms of which patients with sacro-iliac strain suffer vary both in character and degree, according to the severity of the strain, and whether they belong to Type A or B.

In Type A the pain may be mild or severe, so slight as to cause simply an ache across the lumbar and gluteal region on one side, or so severe as to totally incapacitate the patient from

walking, or even lying down. The sciatic nerve passes directly down in front of the sacro-iliac joint, and receives branches from the sacral plexus before it emerges from the sciatic notch. According to the portion of the fiber of the nerve which is pulled upon, whether it be the sciatic, lesser sciatic, or sacral nerves, the pain is referred along these several branches.

Pain in the sacro-iliac joint, therefore, is often felt along the course of the sciatic nerve, even into the calf, and at times into the heel. More often it is referred down the outer aspect of the thigh, and at times it is felt along the crest of the ilium and into the iliac fossa.

Every motion causes pain, and particularly the motions in bending forward or to the side, so that the patient guards them with the greatest care. In the severe cases, the pain and inability to turn is so marked that the patient is not only unable to perform any labor, but is often confined to bed.

In Type B, that of the hollow back, which is most frequently seen in growing girls and neurotic women, the pain is generally referred by the patient to the hollow of the back, and at times as radiating down both thighs. The patients will often describe it as a "tired feeling" rather than an actual pain. Pain of this type is generally worse at menstruation or after unusual exertion or physical prostration. It is also complained of particularly at night, and the patient often sleeps with pillows in the hollow of the back to preserve the unusual lordosis.

Diagnosis.

The diagnosis of sacro-iliac strain is quite simple, but the two types must be differentiated one from the other.

In Type A, where the top of the sacrum is tilted backward, the history is of particular importance, *a history of preceding trauma*, as of a fall, or of being struck by a heavy object in the back, or particularly after some unusual strain on the part of the patient; or, as has been previously stated, the pain has come on after labor.

Pain—referred, acute, or subacute, following and referred along the course of the sciatic, lesser sciatic and sacral nerves.

Pain on direct palpation over the sacro-iliac joint, exerted by pressure from behind. In most cases this pain is elicited on pressure over the upper portion of the joint, but at times it is more pronounced at the lower junction of the sacrum and ilium. Pain may be elicited at times by pressure over both sacro-iliac joints, but generally it is unilateral.

Pain on pressure over the sacro-iliac point in front. Let me call your attention especially to this point, which I have called the sacro-iliac point. It is so often mistaken for McBurney's point that many operations for appendicitis have been erroneously performed on account of its presence. So far as I have been able to gather from the literature, no mention has been made of this point of pain, which is invariably present in all cases of sacro-iliac strain of this type, as well as in inflammatory conditions involving the sacro-iliac joint. It is most constant and is elicited at a fixed point, owing to the structures which cause it, whereas, as we all know, in cases of appendicitis, the pain at McBurney's point may be entirely absent, owing to the wandering proclivities of the appendix.

If the patient is placed on the back, and one makes pressure just to the side and just below the umbilicus, pain will be elicited at that spot on the side in which the sacro-iliac joint is involved.

The next diagnostic sign is the flat back or the obliteration of the lumbar lordosis, due to the tilting of the superior portion of the sacrum backwards, with the third sacral segment as its axis.

Deviation of the Spine.—In bilateral cases there is no deviation of the spine when the patient is in an upright position. But in unilateral cases there is generally deviation of the spine to the side opposite to the sacro-iliac joint involved. This is of marked importance, as it allows us to differentiate the sciaticas which are due to osteoarthritis or infection of the spine, because in this the deviation of the spine is towards the side which is involved.

As the patient bends forward, the deviation of the spine, when present, increases. Bending forward of the spine is more restricted than bending backward, owing to the spasm of the hamstring muscles. Lateral bending of the spine is allowed more freely from the affected joint than toward the affected side.

At times, but rarely, one sees and feels a difference in the amount of prominence of the sacro-iliac articulation on palpation of the sacrum.

Kernig's Sign is Positive.—If one flexes the fully extended leg on the abdomen, the amount of that flexion is naturally limited (Kernig's sign), and pain is referred to the sacro-iliac joint behind. This is due to the contraction and spasm of the hamstring muscles. Kernig's sign is absent in the opposite leg, but at times flexion of the fully extended leg on the abdomen of the good side causes pain referred to the sacro-iliac joint of the bad side.

At times there is an undue mobility which may be made out at the sacro-iliac joint by firmly grasping the ilia in the hands and forcing them together. This, however, is rare, although I have seen it in sacro-iliac strain following the puerperium and in the direct traumatic variety.

There is a total absence of any constitutional features, such as fever, and the blood picture is normal, which would not be the case in certain inflammatory processes of the sacro-iliac joint.

Radiographs.—Whether radiographs will or will not be a help in the diagnosis of the condition, depends upon the type, and whether the strain is bilateral or unilateral. When the condition is bilateral, either in Type A or B, a simple radiograph will not show any deviation of the spine. A stereoscopic radiograph, however, in bilateral cases may show that the articulating surfaces of the sacrum and ilium are out of plumb. In unilateral cases, however, owing to the strain of one joint, the radiograph is a definite adjunct in the diagnosis, for the affected side of the superior edge of the sacrum is tilted not only backward, but also slightly upward, and hence the radiograph will show the spine deviated to the opposite side of the picture. This is due to the list which the top of the sacrum has assumed as a result of the strain.

The diagnostic signs in Type B are different from those in the preceding type. The preceding history of injury is generally absent. It is found mostly in girls between 14 and 20, and in nervous women. The lumbar lordosis, instead of being obliterated, is markedly increased, so that we have the hollow back. The muscular structure is generally below par, both of the spinal and abdominal muscles. Visceroptosis is the rule. The kidneys often are floating and the stomach may lie in the pelvis.

The pain is hardly a pain, but a sense of "always being tired," and tired after slight exertion, or the patient may complain of fatigue when she awakens in the morning. Generally the pain is confined to the small of the back, occasionally going down the thigh a little way.

There is only slight pain to be elicited on direct pressure over the sacro-iliac joint, and rarely can pain be produced by pressing the sacro-iliac joint in the abdomen.

Rarely is there any lateral deviation of the spine, as these cases are almost invariably bilateral, although the pain on one side may be greater than on the other.

Kernig's sign is absent—indeed, flexion of the extended leg generally causes relief rather than pain, as there is no spasm of the hamstring muscles.

Forward bending of the back is not limited, but motion in hyperextension may be restricted.

Pain in most cases of this type is due to the fact that the ligamentous structures of the sacro-iliac joint have to do more than their share of the work in supporting the body. This is due to the weakness of supporting muscles or to direct pull—from pelvic abnormalities or increasing abdominal adiposity.

Differential Diagnosis.—Owing to the drag upon the lumbar and sacral flexors in sacro-iliac strain, the pain is necessarily referred to various portions of the body. It is this fact that so often leads to an erroneous diagnosis.

Tuberculosis of the sacro-iliac joint, in its early stages, offers some difficulty from a differential diagnostic point of view. The pain is situated and referred to such similar localities that other means must be taken to detect it. This can generally be done by keeping in mind the constitutional features of this trouble, with its morning and evening rise of temperature; the blood picture, with its increase in small mononuclear elements; the presence of a cold abscess in the iliac fossa; rectal examination; and the presence of a positive tuberculin reaction, preferably by the subcutaneous method.

Sciatica due to arthritis of the lumbar spine offers some difficulty in differentiation. But this in turn presents an area of tenderness over the lumbar spine on the side of the arthritis. The spine is deviated toward the side of the lumbar arthritis. The X-ray picture shows lipping of the lumbar vertebræ, and possibly deposits of new bone formation. Many cases of sacro-iliac strain have caused these victims to lose their appendices. Pain is often referred down the iliac fossa, and pain at the sacro-iliac point is in many cases mistaken for pain at McBurney's point.

Lumbago is generally a strain of the sacro-iliac joint. We may have a true toxic condition of the muscles of the back, which we call lumbago, but undoubtedly most cases are due to a strain of the sacro-iliac joint.

Symptoms of this disease closely resemble those of certain pelvic conditions. How many uteri have been suspended and how many vaginæ have been tamponned without relief to the patient? Indeed, the symptoms at times so closely correspond that the gynecologist may not realize his mistake until an exploratory laparotomy is done and no cause for the symptoms found.

Treatment.

The treatment which must be instituted to effect a cure in cases of sacro-iliac strain varies according to its severity, and to the type of the case under treatment.

In those cases which we have designated as Type B, when the sacrum is tilted forward, and the pronounced feature is a hollow back, the main principle is to relieve the anterior pulling strain by applying proper support, particularly to relieve the weakened abdominal muscles, and to correct as far as possible the visceroptosis.

In girls and women this can be done by a properly fitting corset, so padded as to support the relaxed stomach and to hold up the floating kidneys. Two extra steels should be incorporated in the corset, on either side of the midline in the back. These steels should not conform accurately to the lumbar lordosis, but tend to diminish it.

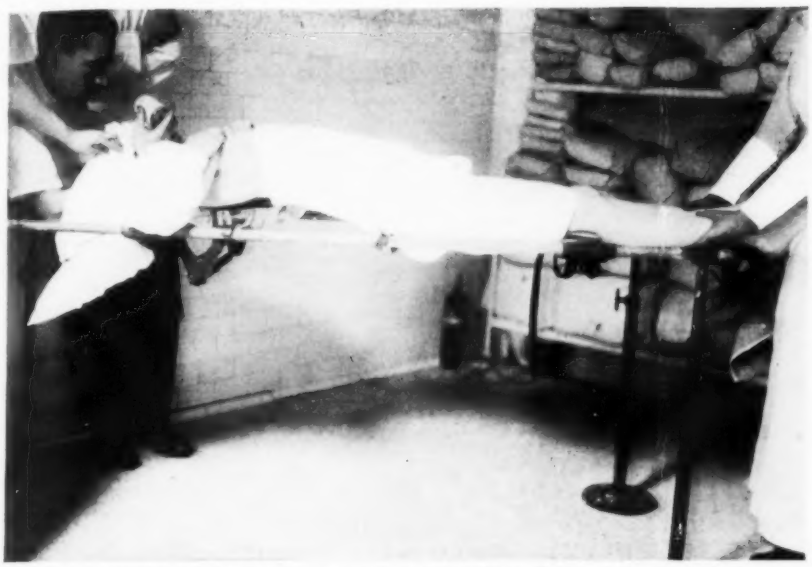
Massage and exercises should be given to the spinal and abdominal muscles, so as to increase their power and so relieve the sacro-iliac ligaments of a portion of the strain. It is needless to say that, when the strain is produced by any intrapelvic condition, it should be remedied by proper gynecological interference.

In cases of this class in men, when the strain is caused by a pendulous abdomen, a proper brace supporting the lower part of the abdomen is of the greatest service.

In Class A, when the sacrum is tilted backward and we have the so-called flat back, the treatment is either supporting or manipulatory, according to the severity and chronicity of the particular case.

In acute but mild cases, both in men and women, the greatest possible relief is given by properly strapping the back. An adhesive strap should be placed, going across the buttocks, after the buttocks have been thoroughly compressed—preferably by an assistant—from one trochanter to the other. These straps should be only about 3 inches in their perpendicular width, and should be placed opposite the third sacral segment. Care must be taken that the straps are kept well below the crest of the ilium. They should not extend in front of the trochanters. This will relieve entirely the mild acute forms of the affection.

In cases of a more chronic type, a more permanent brace should be worn for several months. In males this can be done by a surcingle belt, made of buckskin, about 2½ inches in width, which should firmly encircle the pelvis, on a level with the third sacral segment. In cases of males with a large and fatty abdomen, a brace similar to that described in Class B may be used with much benefit.



PLASTER SPICA APPLIED TO PATIENT WHILE STILL UNDER ANÆSTHESIA.

METHOD OF MANIPULATING A CASE OF SACRO-ILIAC STRAIN UNDER ANÆSTHESIA.

DEVIATION OF THE SPINE IN SACRO-ILIAC STRAIN.

In women the corset may be utilized as a support for a webbing belt which is to go around the pelvis; or a sacral pad, made of steel and padded, which gives pressure over the sacrum by its steel prolongations, may be incorporated into the corset.

In those cases of Type A—both in males and females—which have resisted these mild measures, or in severe cases where the pain is very great, the manipulatory treatment is the method par excellence. It is to this method that I wish particularly to call your attention.

We all know of cases of so-called sciatica, painful in the extreme, which have resisted all therapeutic and surgical treatment for months and months, and cases of chronic invalidism, with constant pain in the thigh and an associated limp. Or, we have seen big, strong, healthy men, hardly able to drag themselves into the office or clinic, so great is the pain and disability. These are the cases which respond immediately to manipulation, to the delight of the operator and to the joy of the patient. I have manipulated 100 of these cases, with immediate relief in almost every case, and with a relapse in only three. The procedure is as follows:

The patient is placed on a low, non-movable table, flat on his back, and then anæsthetized. The anæsthetization should be carried to the point of complete relaxation of all muscular tissue, for the force to be exerted at times is great and muscular rigidity carries with it some danger to the patient.

While an assistant holds the pelvis firmly, the operator grasps the calf of the leg and flexes the fully extended limb. The hamstring muscles are found to be in a state of spasm. They are attached to the tuberosity of the ischium at their proximal end, and to the head of the tibia and fibula at their distal extremity. As the fully extended leg is flexed on the thigh, the hamstring muscles pull on the tuberosity of the ischium and the top of the ilium is pulled backward to meet its sacral junction. This procedure of stretching is carried on until the hamstring muscles are thoroughly relaxed, a condition which is indicated by the fact that the fully extended leg can be flexed to a position far beyond a right angle; indeed, the dorsum of the foot almost touches the shoulder. A definite click is often heard during the manipulation, which some have thought to be due to a replacement of the misplaced sacro-iliac articulation. Of this, however, I am not convinced, for it has seemed to me that the click is to be heard and felt by a slight subluxation of the head of the femur as it pushes against the hamstring while the leg is in extreme flexion. The presence of the click is always synchronous with the release of the hamstring muscles and indicates that the work has been accomplished. If one now looks at the back, one finds that the flat back has been replaced by one with a normal lumbar lordosis. Care should be taken in the manipulation, for it is quite conceivable that, with careless handling, one may obtain a subluxation of the knee joint backward, causing a paralysis, or that one may make a facture of the head of the femur. The only two complications which have occurred in my series of 100 cases have been in one case, the setting up of a femoral phlebitis, and in the other, owing to my inability to make a proper diagnosis, the production some weeks later of a tuberculous abscess springing from the sacro-iliac joint. After the manipulation has been finished, the patient should be placed on a Goldthwaite frame, and put up in a plaster dressing extending from the nipple line down to the knee on the affected side. This is done to preserve the lumbar lordosis which has been obtained by the procedure.

The patient is allowed to remain in this cast in bed for a period of 10 days, when a small pelvic strap, as indicated for the mild forms, is worn as a preventive measure for the next two months.

I know of no class of cases where the results obtained are so pleasing, both to the patient and his physician.

THE MECHANISM AND CLINICAL SIGNIFICANCE OF ANAPHYLACTIC AND PSEUDO-ANAPHYLACTIC SKIN REACTIONS.*

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(From the McManes Laboratory of Experimental Pathology of the University of Pennsylvania, Philadelphia.)

Among the earliest authentic records of what are now regarded as anaphylactic reactions is the description of a skin reaction by Jenner in 1798, who observed the sudden appearance of an "efflorescence of a palish red color" about the parts where variolous matter had been applied to the skin of a woman who had had cow-pox 31 years before. Indeed this astute observer taught that the "disposition to sudden cuticular inflammation," following the application of small-pox or cow-pox matter, may be "effected by the small-pox or cow-pox," and that when this sudden local reaction occurred it might be inferred that the person had had one of these diseases and was not now susceptible to either. Strangely enough, these observations have not attracted the attention they deserve, and even at the present day many physicians fail to recognize or consider the significance of this "immediate or immunity reaction" following cow-pox vaccination among persons who are immune to cow-pox and small-pox, as recently emphasized by Force.

The modern discovery of the local anaphylactic reaction is accredited to Arthus, who discovered in 1903 that the subcutaneous injection of normal serum into sensitized rabbits was followed by a local reaction at the site of injection characterized by inflammatory phenomena, of which edema was a prominent feature. At his time Arthus also showed, that this local reaction was probably an expression of anaphylaxis, inasmuch as these animals would succumb with typical anaphylactic symp-

* Read before The Johns Hopkins Hospital Medical Society, December 4, 1916.

toms following the intravenous injection of the serum. Prior to this time Koch had observed the local reaction following the subcutaneous injection of tuberculin into tuberculous guinea-pigs, but did not suspect the true nature of the phenomenon. In 1907 von Pirquet discovered his tuberculin skin reaction and presented evidence and arguments indicating its anaphylactic nature; since then various skin and mucous membrane reactions have been advocated as convenient and delicate tests for the anaphylactic state to various bacterial and other proteins, in the study of a wide group of pathological conditions.

Whereas the earlier investigations in anaphylaxis were mostly concerned with the clinical manifestations and lesions of the condition, more recently investigators have been mainly interested in the mechanism of the phenomenon and its relation to infection and immunity. For several years my own interests in anaphylaxis have been centered upon skin reactions, and the object of this communication is to present our conceptions of the nature and mechanism of anaphylactic and other skin reactions and their clinical significance as indices of hypersusceptibility and infection, and as indices of resistance to infection or reinfection.

Etiology of Skin Reactions.

Tests for skin reactions are conducted by intradermal injection; by application to an abrasion of the skin; by rubbing into the intact skin or, as on mucous membranes, by mere contact, as instillation into the conjunctival cul-de-sac. In the first and second methods trauma, due to the operation itself, is a factor in the production of the resulting inflammation; likewise the intracutaneous injection of practically any protein or non-protein substance will elicit an inflammatory reaction, providing the dose injected is large enough. The causes of various skin reactions may be summarized, therefore somewhat as follows:

1. The *true* or *specific anaphylactic reaction*, due to the interaction in the skin of specific protein antigen and specific antibody.

2. The *pseudo* or *non-specific protein reaction*, due to the interaction in the skin of general protein substances and non-specific proteolysins.

3. The *traumatic reaction* consequent to the operation; or to the irritant qualities of such substances as preformed bacterial toxins and various preservatives, as phenol and trieresol contained in the injected material.

The intradermal test has proven the most delicate means of eliciting a local anaphylactic response, but is also more likely to yield the non-specific and traumatic reactions.

The Mechanism of the Specific Anaphylactic Skin Reaction.

Although the symptoms and lesions of general anaphylaxis as manifested in man and the lower animals are fairly well understood, the mechanism of the phenomenon cannot be regarded as definitely established; and this is particularly recognized when an attempt is made to correlate the results of an enormous amount of research work in formulating an explanation of the mechanism of the cutaneous anaphylactic reaction.

Furthermore, an acceptable explanation of the mechanism of cutaneous anaphylaxis must include those truly wonderful urticarial-like reactions which follow within a few minutes the application of a very minute dose of anaphylactogen to an abrasion of the skin, as in those exceptional cases of bronchial asthma and extreme hypersensitiveness to horse or other animal protein, and in hay fever to the protein of various pollens. One of my colleagues who is hypersensitive to the protein of the rabbit, guinea-pig and horse, and who suffers with acute asthma when brought into contact with these animals, yields an immediate typical reaction on the skin when the sera of these animals are applied to abrasions, and indeed to the application of a salt solution extract of lint through which he has inspired for 15 minutes the air of a room in which a few of these animals are kept. Similar and more familiar examples of extreme hypersensitiveness to a protein, and the infinitesimal amounts which may produce an anaphylactic reaction, are to be found in the attacks of hay fever due to the inhalation of air and dust carrying the particular pollen. An acceptable explanation of the mechanism of cutaneous anaphylaxis must, therefore, include these immediate reactions to very small doses of anaphylactogen as well as those reactions which follow some hours, and indeed days, after the intracutaneous or subcutaneous injection of much larger doses of protein.

In the first place, are we justified in assuming that the mechanism of general anaphylaxis and that of cutaneous anaphylaxis are identical? This has been the subject of considerable research over a period of several years in attempts to transfer the specific antibody in animals yielding positive skin reactions to normal animals; by testing animals sensitized at the same time and in the same manner, by the skin test and others, by the intravenous injection of the intoxicating dose of protein; and by first applying the skin test, and after 24 hours injecting the same animals intravenously. The majority of these experiments were conducted with tuberculins and with divergent results and interpretations, but there appears to be sufficient evidence at hand to indicate that a local skin reaction may be an expression of an anaphylactic state to a certain protein, and this is accepted as established in this discussion, although there are not sufficient data at hand to prove that the mechanism of the local or skin anaphylactic reaction is identical with that of the general and fatal reaction following intravenous injection.

At the present time two main theories on the mechanism of anaphylaxis are prominently before us: (1) The humoral or chemical theory, which maintains that the lesions and symptoms of anaphylaxis are due to a poison derived from a protein matrix through the interaction of anaphylactogen and its antibody, or a ferment in the blood and variously designated proteotoxin, anaphylatoxin and serotoxin; and (2) the physical or cellular theory, which denies the formation and activity of this protein poison and maintains that the anaphylactogen unites with its antibody in the cell, and that this union results in a disturbance causing shock of the cell.

The two schools agree at least in two points, namely, that an antibody is concerned in the phenomenon of anaphylaxis, and that the anaphylactogen is always of a protein nature. Neither has very clear conceptions of the nature and mechanism of action of the antibody; whereas the adherents of the cellular theory maintain that the foreign protein constitutes the anaphylactogen, the adherents of the chemical theory, are divided in their opinions regarding the protein matrix, some regarding the matrix as the foreign protein and others as the protein of the patient's own serum.

The older conception of the antibody, that held by Friedberger, and widely accepted to-day, is to the effect that it belongs to Ehrlich's group of amboceptors or lytic antibodies of the third order. As is well known, an antibody of this nature, according to Ehrlich's theory, is produced through the influence of the antigen (bacteria, serum, egg albumen, pollens, etc.) upon the body cells, and is specific for the antigen in so far that it will unite only with its antigen and prepare the latter for the disrupting, digesting or lytic action of a ferment-like substance normally present in the blood and called complement. In this manner the antibody producing the protein poison of anaphylaxis has the same structure and acts in the same manner as other well-known antibodies of this order, namely, the hemolysins and bacteriolysins.

According to this view we must concede that complement plays a rôle, indeed a most important one, in the production of anaphylaxis. While complement has properties suggestive of a proteolytic ferment, we know little or nothing of its true nature beyond that it is regarded as essential for the cleavage of the antigenic molecule. Sleeswijk,[1] Friedberger and Hartoch,[2] Loeffler[3] and others have shown that complement is diminished during anaphylactic shock; likewise Friedberger,[4] making use of the observations of Nolf[5] and Hektoen[6] to the effect that complement is not bound by antigen and antibody in the presence of hypertonic salt solution, devised experiments which appeared definitely to establish the rôle of complement in the production of a protein poison and in the mechanism of anaphylaxis.

Test-tube experiments, and particularly efforts to explain anaphylaxis on the basis of the Abderhalden theory and technic, seriously question the rôle of complement in the mechanism of anaphylaxis. Williams and Pearce,[7] Lange,[8] Jobling, Eggstein and Petersen,[9] and Kolmer and Williams,[10] found that digestion occurred with activated serum, but to a lesser degree than results with active serum. On the other hand, Stephan,[11] Hauptmann,[12] Bettencourt and Menèzes[13] and Steisung[14] believe that a complement plays a very important rôle in Abderhalden's test. Abderhalden, himself, while believing that the serum complement plays some part in the mechanism of his reaction, but in a different manner than in hemolysis or other cytolytic reactions, offers no adequate explanation of its relation to these processes.

It would appear, therefore, that if we attempt to explain anaphylactic reactions, either general or local, by an application of the well-known theory of antigen-amboceptor-complement production of the anaphylactic poison on the basis of experiments *in vitro*, we must prepare ourselves to believe that the actual lytic or digestive body in the serum (call it complement or true enzyme) exists in both a thermolabile and thermostabile condition. Whereas hemolysis, bacteriolysis and other cytolytic reactions will occur only in the presence of fresh complement serum, the protein poison of anaphylaxis may be produced apparently by an active or an inactivated serum; otherwise it would appear that an explanation of the mechanism concerned in the production of anaphylatoxin must be withdrawn from the field of amboceptor-antigen-complement activity, as understood at present.

Vaughan has always called the antibody in the serum concerned in the mechanism of anaphylaxis a "ferment"; likewise Abderhalden and Jobling and Petersen have used this term. As far as I know, these observers have not clearly defined the meaning of the term "ferment"; nor have they established its relation or lack of relation to the amboceptors of Ehrlich or sensitizers of Bordet; apparently they regard the "ferment" as a proteolytic enzyme or protease. This conception of the enzyme nature of the "ferment" would correspond somewhat with the non-specific alexin of Bordet, or Ehrlich's complement, and fail to harmonize with the specific nature of anaphylaxis. Otherwise it is necessary to believe that the entrance of a foreign protein calls forth the production of a specific proteolytic enzyme or ferment capable in itself of attacking and disrupting a protein matrix, and, as stated above, to place the mechanism of anaphylaxis out of the realm of amboceptors and complements according to the theories of Ehrlich and Bordet.

The trend of more recent work in the mechanism of anaphylaxis by Jobling and Petersen[15] is in this direction. These investigators have produced a protein poison *in vitro* by chemical methods in such manner as apparently to rule out the influence of the thermolabile and easily destroyed complement or alexin. According to their views, serum complement and normal proteolytic ferments are not identical and, whereas the former may be inactivated by heating at 56° C. for half an hour, the latter are more resistant, the increased digestive power observed following the addition of serum complement to inactivated pregnancy serum being ascribed to the amounts of non-specific protease thereby added.

It is clear, therefore, that in the humoral or chemical theory of anaphylaxis the true nature of the antibody is unknown and in dispute: Friedberger[16] was among the first to maintain that the antibody is identical with precipitin. More recently, Lake, Osborne and Wells,[17] Doerr and particularly Weil,[18] the last being an ardent advocate of the cellular theory of anaphylaxis, are inclined to the same view without, however, offering a clear explanation of its action *in vivo* in the mechanism of anaphylaxis. While the rôle of precipitins themselves appears to have been excluded as directly participating in the production of anaphylactic shock, recent experiments by Zinsser[19] and others would tend to show that a precipitin possesses the nature of a protein sensitizer or antibody that sensitizes or prepares the protein antigen for lysis or destruction.

As previously stated, the chemical and cellular theories of anaphylaxis agree that the anaphylactogen is always a protein. In the cellular theory the anaphylactogen is regarded as specific, and this is in accord with accepted facts regarding the high specificity of the anaphylactic reaction; in the chemical theory, however, there is no agreement, some maintaining that the anaphylatoxin is derived from the foreign poison or anaphylactogen, and others that it is derived from the protein of the patient's own serum.

The view first held in the chemical theory is that in the anaphylactic reaction the antibody acts upon its protein antigen in a specific manner and produces in the reaction the protein poison or anaphylatoxin responsible for the lesions and symptoms of the anaphylactic reaction. For example, during an infection with the spirocheta pallida, an antibody is produced which, acting upon an emulsion of dead spirochetes (luetin) injected into the skin, splits the protein of these parasites in a specific manner with the production of a poison responsible for the local reaction of erythema and infiltration.

An anaphylactic reaction of this kind, a cellular or formed antigen being employed, is regarded as being divided into two phases. As compact structures, cells cannot enter into direct chemical relations with the fixed tissue cells until they have been resolved or disintegrated into simpler constituents by ferments or antibodies in the body fluids. This is followed by the second phase, or the interaction of the anaphylactic antibody and the dissolved antigen. Anaphylactic reactions with such formed elements as erythrocytes and bacteria may occur; usually it is more difficult to sensitize the body cells with these antigens than when dissolved proteins, as in blood serum, are employed.

The experiments of Keysser and Wassermann,[20] Bordet,[21] Jobling and Petersen,[22] Plaut,[23] Peiper,[24] Friedemann and Schönfeld,[25] Bronfenbrenner,[26] and others, tend to show that the mechanism is not quite so simple and direct, and that a protein poison may be produced in the absence of the specific antigen. They have demonstrated by experiments *in vitro* that such inert substances as kaolin, barium sulphate, agar or indifferent bacteria or precipitates may replace the antigen in the production of a protein poison. Since the presence of protein substances could be excluded, as with such inorganic substances as kaolin and barium sulphate, the conclusion was naturally drawn that the matrix of the poison was not the antigen or substrate, but the constituents of the serum itself. Jobling and Petersen advanced the theory that the proteolytic ferment was held in check by antiferments (largely the unsaturated fatty acids in serum), and that these substances, as kaolin or barium sulphate, absorb the antiferments and thereby release the proteolytic ferments which proceed to digest the protein of the serum. For this reason these investigators have applied the name "serotoxin" to the protein poison as indicating its source.

Applying these observations and views to the subject under discussion, it would appear necessary to infer that the antigen is non-specific and acts as it were in a purely mechanical manner; this does not at all agree with the great mass of data showing the highly specific nature of anaphylaxis. In tertiary syphilis, for example, the reaction in the skin following an injection of an emulsion of dead spirochetes (luetin) would be due, according to this mechanism, not to a digestion of the protein of the spirochetes with the production of a protein poison, but the luetin would act simply as a local absorbent of the antiferment, releasing thereby proteolytic ferments which proceed to digest the patient's own serum or cellular protein *in loco* with the production of a poison responsible for the reaction; and if this were true, the reaction lacks specificity.

Bronfenbrenner[27] explains the specific production of anaphylatoxin by non-specific ferments or antibodies as follows:

Specific antibodies are produced, and the combining of these with the antigen causes a falling out or inactivation of the antiferments of the serum by a change in colloidal conditions resulting in the release of normal or non-specific proteolytic ferments which disrupt or digest the protein of the serum. In other words specific antibodies are produced, but instead of these digesting the protein of the antigen or of the serum directly, they act by uniting with the antigen, and this union results in the removal of anti-enzyme, thereby releasing or rendering active the normal and non-specific enzymes of the serum which produce a protein poison or anaphylatoxin, by digesting the protein of the serum.

Whether or not the results of a study of the mechanism of Abderhalden's reaction—which in the final analysis is nothing more than a popularized method of studying protein digestion in a manner pregnant with opportunities for error—can be applied to unfolding the mechanism of anaphylaxis is uncertain; but it is certain that an explanation of the mechanism of either the local skin or general anaphylactic reaction must satisfactorily explain the high and uniform specificity of these reactions before it is acceptable.

The above-mentioned experiments, which have been largely conducted *in vitro*, are not without definite value and, as I shall point out later, have a greater bearing upon the mechanism of the pseudo than upon the true anaphylactic reaction and the phenomena of local inflammation in general.

Up to this point our discussion has been confined to present-day conceptions of the nature of the protein matrix, the mechanism of action of the antibody or ferment according to the clinical theory, and the effects of the protein poison on body cells in anaphylactic phenomena.

No discussion is complete, however, without particular reference to that peculiar change on the part of the cells, probably involving the colloidal chemistry of the cells themselves, which exerts so important a rôle in anaphylaxis, and particularly in the local reaction. This altered reactivity of the cells, or their unusual and exaggerated susceptibility to the effects of the products of digestion of foreign proteins, was early emphasized by von Pirquet, by Rosenau and Anderson, and by other pioneers in this field; and on account of the importance of this phase the former proposed the term "allergy," meaning "altered reactivity," as describing the phenomena more concisely than Richet's term "anaphylaxis," meaning "without protection." The term "allergy" is in our opinion more

appropriate, as it emphasizes the important hypersensitiveness or altered reactivity of the cells, regardless of any theories we may entertain as to the manner in which this change is brought about or manifested.

Definite information on the nature of this peculiar cellular change is lacking. When one bears in mind the intense local, focal and general reaction in tuberculosis that may follow the injection of a minute amount of tuberculin, or the minute amount of protein that suffices to induce the anaphylactic reaction in the classical experiment with horse-serum and guinea-pigs, conditions in which the amount of protein poison produced must be very slight indeed for physical reasons alone, the supposition is forced upon one that some change rendering the cells highly susceptible to the anaphylactic poison is of fundamental importance in anaphylactic reactions.

Investigators have attempted to explain this peculiar hyperactivity of the body cells on the basis that the reaction is a cellular one, that is, that the antibody is within the cell and that the antigen-antibody reaction occurs in this position rather than in the blood-stream by means of free or circulating antibody and antigen. According to the "cellular theory," if the serum of an immunized animal containing the anaphylactic antibody is injected into a normal animal (passive anaphylaxis) and is followed by an injection of the antigen, an anaphylactic reaction cannot occur before the elapse of sufficient time for the antibody to become anchored to cells. The "humoral theory," on the other hand, assumes that the antigen meets the antibody in the blood-stream and explains the time required between the injection of immune serum and antigen in passive anaphylaxis as due to a failure of rapid union between antigen and antibody, unless quantitative relations between the two are accidentally correct.

The early theory of Friedberger,[16] explaining anaphylaxis on the basis of "sessile receptors"; the experiments of Friedberger and Girgolaff,[17] who passively sensitized normal animals by transplanting the thoroughly washed organs of a sensitized animal; the transfusion experiments of Pearce and Eisenbrey,[19] who transferred the blood of a sensitized animal to a normal animal, and the blood of a normal animal to a sensitized one, finding that the latter, but not the former, reacted when the antigen was injected as soon as the transfusions were completed; the work of Coca,[20] who found that sensitized guinea-pigs would still react after being thoroughly bled and perfused with salt solution; the investigations of Schultz,[21] Dale,[22] and particularly of Weil,[23] showing that the excised and washed muscles of sensitized animals would react *in vitro* in a bath of Ringer's solution when the antigen was added, support most strongly the cellular theory of anaphylaxis as emphasized also in the work and recent communications of Doerr.[24]

In the opinion of Weil, Doerr, Bayliss, Coca and others, the "cellular" theory is the only tenable one to-day. According to this theory of anaphylaxis, the antibody is in or on the body cells; upon union with the antigen, the cells undergo a physical shock which has been likened to an electrical shock, and this constitutes the basis of the anaphylactic reaction without the formation of any intermediate or chemical poison.

As emphasized by Weil,[25] there is no direct evidence of the production of a chemical poison or anaphylatoxin during or after an anaphylactic reaction in the living animal. This poison has not been satisfactorily demonstrated in the blood and in animals recovering from a general anaphylactic reaction, the phenomena being more suggestive of a transitory "shock" than of an intoxication with a chemical poison.

On the other hand, the mass of experimental evidence indicating that the anaphylactic reaction is not purely cellular, but at least in part an intravascular reaction, is too strong to be discarded. As pointed out by Zinsser and Young,[26] the necessary time usually required in passive anaphylaxis between the injection of immune serum and antigen may be due to slow union between antigen and antibody in the blood-stream, on the basis that the anaphylactic reaction involves the interaction of colloids and that a protective colloid is responsible for the slow union of antigen and antibody, unless its influence is obviated by exact quantitative proportions between antigen and antibody, which under experimental conditions may be secured in a more or less accidental manner.

As antibodies are produced by the body cells, it is reasonable to believe that they are present in the protoplasm of the cells, and even after thorough washing of the tissues are capable of union with their antigen. It is entirely likely that these attached or sessile antibodies are chiefly concerned in the phenomena of anaphylaxis, but I cannot subscribe entirely to the cellular theory, because of the mass of experimental data bearing on the production of the protein poison, particularly *in vitro*, by the free antibodies in an immune serum. The reactions *in vivo* of hemolysis and bacteriolysis, which are lytic processes, apparently similar to those concerned in anaphylactic reactions, are probably intravascular processes; it is also likely that in anaphylaxis to formed antigens the first phase of the reaction, that is, the disruption of the antigenic cell, is intravascular, showing that lytic reactions entirely analogous to our conception of the mechanism of the production of the protein poison in anaphylactic reactions may occur in the blood serum. For these reasons alone I cannot exclude the free antibodies in the blood from playing some rôle in the phenomena of anaphylaxis.

The extreme sensitiveness of the body cells in anaphylaxis to the protein suggests to me that the cells acquire the property of union with the protein poison to an extreme degree, as if they were furnished, as a result of the initial dose of foreign protein, with an increased number of specific and sessile receptors for the protein poison. In other words, while the protein poison may be produced in the cells by sessile receptors, or in the blood-stream by free receptors, anaphylaxis itself, that is, the hypersensitiveness of the cells is due to the increased binding power of the cells for the protein poison. In our opinion this in part explains true allergy, that is, the effects of local or general sensitization (production in the protoplasm of the cells of increased receptors for the protein poison) and the immediate well-marked or even violent effects following the production of what must be very minute amounts of protein poison, as in the cutaneous tuberculin reaction, or in the

classical horse-serum reaction in guinea-pigs following the intravenous injection of the intoxicating or second dose of protein in very minute or infinitesimal dosage.

Personally I should be more prepared to understand and accept the cellular theory in the strictest sense in the mechanism of anaphylaxis, were my studies confined entirely to general anaphylactic shock; in the local reaction, however, the slowly spreading character of the lesion, the erythema, edema and eosinophilic infiltration strongly suggest that a diffusible irritant has been produced similar, in some respects at least, to that which can be produced *in vitro*.

As far as I am aware, the skin or local anaphylactic reaction has not been explained on the basis of the cellular theory alone in its strictest sense. These reactions have many of the features of an inflammatory reaction, of which vascular changes (hyperemia) and edema are prominent features. Intracutaneous reactions are likely to persist for several days; likewise the cutaneous tuberculin reaction, although the cutaneous reaction to pollen and serum may reach its height within half an hour and disappear within a few hours. May these inflammatory-like changes be ascribed to a temporary and physical shock of the endothelium of vessels in the skin, followed by stasis and exudation, and of the connective-tissue cells at the site of injection? As previously stated, I believe that the cells play the major rôle in anaphylaxis, in that the formation of a diffusible protein poison occurs largely in or on the cells by reason of the fact that the antibodies are largely situated in the cells and that the cells bear the brunt of the change and undergo shock by reason of the poison being produced in them, but I also believe that a poison is produced which may escape detection by high dilution in the body fluids in the general reaction, but which appears in the local reaction as a diffusible irritant, producing the phenomena of acute congestion, edema and leucocytic infiltration (particularly of eosinophiles).

It is my opinion that the source of the protein poison in true anaphylaxis is always that which has been injected and for which specific antibodies are present mainly in the cells.

I regard cutaneous anaphylaxis as due to an interaction between true or specific antigen and its specific antibody with the production of a diffusible irritant capable of exciting inflammation; that this union of antigen and antibody occurs principally within the cells, and that the cells suffer largely by reason of this interaction and formation of irritant within them.

An adequate explanation of those apparently anaphylactic reactions to drugs has not been made. It is generally held that the drug alters a body protein with the formation of a new protein compound capable of sensitizing and producing anaphylaxis. Recently my colleague, Dr. Fred Boerner, who is hypersensitive to quinine and suffers considerably with cutaneous manifestations, if even minute doses are swallowed, has shown me a marked reaction of edema and erythema in his skin following in a few minutes the application of powdered quinine sulphate or a solution of the bisulphate to an abrasion. He has shown that this reaction is apparently specific, inasmuch as it does not occur among persons not hypersensitive to quinine, and a similar reaction occurred in the skin of a second person known to be hypersensitive. The occurrence of these reactions within a few minutes after the application of quinine renders the theory of the formation and activity of a new protein compound doubtful.

Mechanism of Non-Specific Protein and Traumatic Skin Reactions.

It appears well established that the blood-serum, leucocytes and the fixed cells of various tissues of the body contain proteolytic ferments capable of digesting various protein substances *in vitro*. The digestive activity of these ferments can be studied and determined only by very delicate methods, and are apparently non-specific in character.[21] *In vitro* they apparently are capable of producing toxic substances which may be regarded as protein derivatives. These proteolytic ferments may be responsible for local inflammatory phenomena, and in an attempt to correlate these results with the mechanism of the non-specific and purely inflammatory reaction which may be the sole reaction in the skin and lead to misinterpretation and error, or occur coincidently with the true anaphylactic reaction, the following explanations have been offered:

1. An irritant is produced through the interaction of general proteolytic ferments and various proteins injected, as those contained in broth, agar or ascitic fluid. This irritant or chemical poison is responsible for the lesion.

2. Trauma caused by the needle, or trauma plus injury to the cells, due to the presence of a preservative as phenol or trieresol, or a preformed toxin (as the diphtheria toxin used in the Schick test), or a bacterial protein of an irritant nature, may destroy a sufficient number of cells to release their proteolytic ferments which proceed with a process of digestion; or the injection mass and dead cells mechanically absorb the antiferment and thereby activate the ferments which produce from the injected protein, or that of the dead cells and patient's own serum, sufficient proteotoxin to bring about an inflammatory reaction.

The injection into the skin of a foreign protein (the anaphylactogen) as that protein present in sterile bouillon or, for example, the protein of bouillon, agar and spirochetes as present in luetin, increases the production of protein poison by more active release of proteolytic ferments through removal of the antiferments by absorption or in some other way, followed by digestion of the injected protein and the protein of the patient's devitalized cells and serum.

This protein poison or proteotoxin is an irritant and excites inflammation of varying degrees of severity. In this manner we have a ready explanation for those pseudo-reactions following the intracutaneous injection of sterile broth, as found by Kolmer and Moshage,[38] of extracts of placental cells by Engelhorn and Wintz,[39] Falls and Bartlett,[40] Kolmer and Williams,[41] of agar and emulsions of normal and pathologic skin by Stokes,[42,43] of heated diphtheria toxin-broth by Zingher,[44] and various other protein substances by various investigators.

It is highly probable that the quantity of proteolytic fer-

ments in the cells and serum of different persons vary, and that the quantity of ferments in the cells of the skin of the same person varies in different areas of the body; and in this manner could be explained the varying degrees of non-specific or purely inflammatory reactions in the same person in different parts of the body, or among different persons, after the injection of the same protein in the same dosage. Dr. Moshage and I have found that the skins of persons convalescent from scarlet fever and measles are especially prone to yield these non-specific reactions.

Any protein substance, if injected into the skin in sufficiently large amount, will elicit a non-specific or inflammatory reaction. For this reason the material used in conducting skin tests for the specific anaphylactic reaction should be carefully prepared and administered in such amount as will not elicit a non-specific reaction among a large number of controls; and the injection of a control fluid is always advisable. Cutaneous tests are much less likely than intracutaneous tests to yield non-specific reactions of sufficient degree to prove disturbing; they are less delicate tests for the anaphylactic state, but also less open to error.

The Influence of Drugs Upon Skin Reactions.

Recently Sherrick [49] has reported that normal persons under the influence of iodides would yield positive reactions to the intracutaneous injection of luetin. Broadwell, Matsunami and I [50] were able to confirm these observations, in that a normal person who had reacted negatively to luetin in the preliminary test would frequently react to a well-marked degree when the test was applied after the administration of potassium iodide. We also observed similar results among rabbits and guinea-pigs.

During the past year these studies have been continued with the cooperation of Dr. Immerman, Dr. Matsunami and Dr. Montgomery,[51] various iodides, bromides, chlorides and anesthetics and two intracutaneous tests, namely, the luetin test and one with an emulsion of *B. prodigiosus* being employed. Both tests were made beforehand upon Wassermann-negative persons, and repeated after the administration of from 90 to 170 gr. of the drugs, or after operation under ether or nitrous oxide. Iodides and bromides were found to exert a considerable influence, whereas the influence of chlorides was much less in evidence, and ether and nitrous oxide were without demonstrable effect.

According to Jobling and Petersen, the antiferment of the serum is of the nature of unsaturated fatty acids, and these may be removed by the halogens and the ferments thereby released or rendered active. The influence of these drugs upon skin tests may, therefore, be explained upon this basis. We are of the opinion that they do not influence the mechanism of true anaphylactic reaction, but only the non-specific or simple inflammatory portion of a skin reaction by facilitating the release of non-specific ferments. This opinion is based upon the observation that the influence of these drugs upon skin reactions has been observed in persons who were not anaphylactic to the protein; that much less influence was observed upon true anaphylactic reactions to the cutaneous application of tuberculin, and that the greater the amount of bacterial protein or culture medium constituents injected the severer the reaction.

Since the non-specific element may always play a part in skin reactions following intradermal injections, it is well for physicians to bear in mind that these drugs may so favor the non-specific reaction as to present evidences of a violent reaction which may be interpreted as anaphylactic.

The Clinical Significance of Anaphylactic Skin Reactions.

1. *As Indices of Hypersusceptibility and Infection.*—The clinical significance of a true anaphylactic skin reaction to a certain protein, aside from establishing the fact that a person is hypersensitive to that protein, depends upon what harm may be done with the enteral or parenteral introduction of the protein. It is not my purpose to review in detail the many clinical conditions which appear to be due to a state of anaphylaxis; this phase of the subject has been recently covered in a through and excellent manner by Longcope.[52] Here it may be recalled that examples of apparently true spontaneous hypersensitiveness to various foreign proteins are not uncommon and, indeed, the trend of recent investigations is always widening this field and establishing hypersensitiveness as a probable basis for many diseases with symptoms referable to the respiratory tract, gastro-intestinal tract, and the skin. In the minds of not a few physicians the term "anaphylaxis" means a brief and stormy general reaction following the administration of diphtheritic antitoxic horse-serum, a reaction occupying, as it were, a distinct and isolated place in the field of immunity, whereas this is but one manifestation of a process which bids fair to become established as the basis of many and diverse clinical conditions, as, for example, hay fever, ivy poisoning and similar toxic dermatoses, bronchial asthma, serum sickness and that wide field of various food idiosyncrasies due to the ingestion of eggs, milk and various meats as studied by Schloss,[53] Lesné and Richet,[54] Talbot,[55] Smith,[56] Strickler,[57] Blackfan,[58] and others. I have been particularly interested in the investigations conducted in my laboratory by Strickler, which show the very important relation of hypersensitiveness to various vegetable and animal proteins to eczema and other skin diseases.

Further researches will show us what harm may be done by the anaphylactic poison; at present we know that grave symptoms and even death may result from the parenteral injection of a serum to which a person is highly susceptible; Longcope and his co-workers have shown that the poison may produce slow but definite degenerative lesions in the kidneys; the ingestion of eggs or other food by a person hypersusceptible to their protein is known to produce symptoms and skin manifestations which disappear or are ameliorated upon the permanent withdrawal from the diet of such foods. In other words, evidence is accumulating to show that hypersensitiveness plays an active rôle in the etiology of many diseases, and in the detection of

these skin reactions are proving of great value and indeed may prove the only means of specific diagnosis.

As is well known, anaphylactic skin reactions may be elicited in various bacterial and protozoan diseases with anaphylactogens prepared from the protein of the respective microparasites, particularly in tuberculosis, glanders, typhoid fever and syphilis. Well-marked and specific reactions have also been found by Amberg [59] and by Kolmer and Strickler in ring-worm and favus, and isolated reports show that they may be elicited in various other diseases with proper preparations.

In these conditions, however, the skin reactions are not always elicited, and especially during the early and acute stages. An interval of time is required for the purpose of sensitization, and during the acute stages antigen and antibody may both be present in the cells and body fluids, as shown by Weil [60] and Denzer,[61] with continual interaction expressed in the symptom-complex of the infection, and thereby giving no response when the protein is applied or injected into the skin. Furthermore, the chemical nature of the protein of our anaphylactogen may have been altered in the course of preparation to a sufficient extent to fail to elicit an anaphylactic reaction. These and other factors not understood diminish the practical value of a skin test. At present, however, it may be stated that they possess a diagnostic value which is particularly high in chronic infections, and that no other satisfactory clinical or laboratory test for the state of anaphylaxis to a particular protein and for the anaphylactic antibody has been discovered, except that by which the protein is actually brought into relation with the body cells, as in the parenteral introduction of the protein. Of great interest in this connection is the relation of the intensity of the anaphylactic skin reaction to the extent of the infection. Krause [62] has recently studied in a thorough and excellent manner the tuberculin skin-reaction in relation to experimental tuberculosis, finding that cutaneous hypersensitiveness to tuberculo-protein is inaugurated by the establishment of infection and the development of the initial focus; that the skin-reaction increases with progressive disease; is diminished with healing and increased by reinfection.

2. *As Indices of Immunity.*—Of further importance is the question of the clinical significance of a local anaphylactic reaction as an index of immunity, that is, resistance to an infection or reinfection. Is the anaphylactic antibody capable of attacking and destroying the antigenic protein in a living state? Are protective and curative antibodies produced by the defensive mechanism of the body, while the cells are being sensitized and the anaphylactic antibody is being produced? In other words, is hypersensitiveness to be regarded as an index of resistance?

In 1798 Jenner wrote: "It is remarkable that variolous matter, when the system is disposed to reject it, should excite inflammation on the part to which it is applied more speedily than when it produces the small-pox. Indeed, it becomes almost a criterion by which we can determine whether the infection will be received or not." In other words, as previously mentioned, this astute observer noted that a person who presented within a few days at the site of vaccination an "efflorescence of palish color" was probably immune to small-pox. Force [63] has recently drawn attention to this "immediate" reaction to inoculation with cow-pox virus as an evidence of resistance or immunity to cow-pox and small-pox, and my own experience supports his conclusions. Here, indeed, we have evidence at hand indicating that an anaphylactic state is an index of the coincident presence of antibodies and resistance.

Investigations bearing upon the relation of anaphylaxis to immunity in other infections have not generally yielded these results. Rosenau and Anderson [64] sensitized pigs with extracts of *B. typhosus* and *B. coli*, and found that animals so treated were immune to amounts of the respective microorganisms fatal to normal pigs; Romer [65] and Sata,[66] in experiments among cattle with *B. tuberculosis*, reached the conclusion that a state of hypersensitiveness meant a certain degree of resistance, while Krause [66] and Austrian [67] have expressed the opinion based upon experiments, that sensitization of non-tuberculous animals with tubercle protein does not raise their resistance to experimental tuberculosis infection and indeed may lower it.

More recently Gay and Force [68] have greatly renewed interest in this subject by advocating the skin test as a means of determining defensive activity following typhoid fever or active immunization by means of vaccines. Their first work was conducted with a "typhoidin" prepared in the same manner as Koch's old tuberculin by cutaneous inoculation. Later, Gay and Claypole [69] prepared typhoidin by precipitating the solution with alcohol, washing the precipitate with alcohol and ether, drying in a vacuum and suspending the resulting powder in phenolized normal salt solution, which was injected intracutaneously and applied cutaneously, a control powder being prepared from broth and used in the same manner. With this skin test, Gay and his associates have studied the relative value of various vaccines and regard the anaphylactic reaction as indicative of a state of immunity. Nichols [70] has questioned the value of the anaphylactic skin test as an index of immunity and regards the typhoidin reaction as indicating nothing more than sensitization to typhoid protein, which is apparently less lasting and less specific than the true immunity to this infection. He bases this opinion on the fact that in his experience the typhoidin skin test gave fewer positive reactions (75 per cent) than were generally expected, since about 90 per cent of persons who have had typhoid fever are immune for many years, or even for the balance of life. Furthermore, according to Nichols, experience has shown that protection following typhoid fever is of longer duration than is indicated by the typhoidin test, and although a large percentage of persons who have had typhoid fever or have been immunized with typhoid vaccine react to paratyphoidin, recent experiences and statistics, particularly in Europe, have indicated that these persons are not immune to paratyphoid fever.

My own experiments in this field have been largely tests *in vitro* for various antibodies as agglutinins, bacteriolysins and complement-fixing substances in the fresh sterile blood sera of persons hypersensitive to various proteins, in order to determine whether or not the state of hypersensitiveness to a particular bacterial protein was accompanied by demonstrable

amounts of these antibodies. I am well aware of the shortcomings of such tests and that the weight of opinion minimizes their value as an index of actual immunity. As previously mentioned, Friedberger[16] was among the first to maintain the identity of precipitin and the anaphylactic antibody; Doerr and Russ[17] independently reached the same conclusion, and more recently Lake, Osborne and Wells[18] and Weil[19] have brought forward a considerable amount of evidence in support of the view that precipitins are frequently present in the serum of the sensitized animal.

The experiments conducted by Mr. Berge and the author[20] with reference to the typhoidin skin reaction showed that while the bactericidal power of human serum over *B. typhosus* is increased in a proportion of persons following typhoid fever or active immunization with a vaccine, there is no direct relation between the typhoidin skin reaction and the results of bactericidal tests *in vitro*. Likewise, no definite relation was observed between the presence of agglutinins and complement-fixing antibodies and the skin reactions.

A similar study in syphilis by Broadwell and the author[21] has shown that in human syphilis spirocheticidal antibodies for culture pallida are practically absent from the sera of those persons who do and who do not react to the intracutaneous injection of luetin. Likewise, no constant relationship was found between the occurrence of cutaneous hypersensitiveness to luetin and the presence of agglutinins for culture pallida and of a complement-fixing antibody with an antigen of luetin.

Similar studies in diphtheria by the author[14] likewise showed an absence of any relationship between cutaneous hypersensitiveness to a polyvalent and detoxized emulsion of diphtheria bacilli or diphtherin,[22] and the presence of such antibodies as antitoxin, agglutinin, bacteriolysin and complement-fixing substances for diphtheria bacilli.

Additional studies by Harkins, Matsunami and the author,[23] along similar lines in canine distemper, have shown that the sera of dogs reacting positively to the intracutaneous injection of a polyvalent emulsion of *B. bronchisepticus*[24] do not show the presence of agglutinins, bacteriolysins and complement-fixing antibodies for this bacillus in any constant relationship to the skin reactions.

In a strict sense the question whether or not an anaphylactic skin reaction may be taken as an index of defensive activity can only be answered on the basis of actual protective experiments. Time alone will tell whether or not the person presenting a positive reaction to typhoidin is actual immune to typhoid fever as claimed by Gay and his associates. Experiments among rabbits with cultures of *Spirocheta pallida* by Noguchi,[25] consisting in the immunization of the animals until they reacted to the intracutaneous injection of luetin, followed by an actual test of their immunity to living virulent spirochetes by inoculating the testicle, have given Dr. Noguchi the impression that the immunization reduced susceptibility in some rabbits, whereas it had no effect whatsoever in others, and indeed seemed to render some more susceptible. Furthermore, it is highly probable that the syphilitic is open to reinfection with *Spirocheta pallida;* certainly our experiments failed to show the presence of appreciable amounts of spirocheticidal antibodies in the sera of tertiary syphilitics reacting positively or negatively to the intracutaneous injection of luetin, and it is highly probable that the luetin reaction does not indicate resistance to reinfection or the "lighting up" of a present infection.

Furthermore, I have seen three persons presenting perfectly typical reactions to diphtherin contract diphtheria, and dogs that have reacted to bronchisepticin have contracted canine distemper.

The sum total of these studies indicates that, although antibodies that may be regarded as possessing protective and curative properties toward a certain protein *may* be present in the body fluids of persons and animals hypersensitive to this particular protein, the condition of hypersensitiveness in itself is no direct evidence of their presence or of resistance to a particular infection, although these antibodies are most likely to be present in the body fluids of those persons who are hypersensitive. The positive anaphylactic skin test is therefore, evidence of infection or sensitization to a particular protein without bearing any direct relation to resistance to infection or reinfection.

The clinical significance and practical value of skin reactions are largely of a diagnostic nature for the detection of hypersensitiveness to a protein or proteins which may, when introduced into the organism, produce various acute or chronic lesions and symptoms of disease.

Clinical Significance of the Spurious or Non-Specific Protein and Traumatic Skin Reactions.

At the present time the chief clinical significance of the pseudo-anaphylactic and traumatic skin reactions is the likelihood of mistaking them for true anaphylactic reactions.

The Schick toxin reaction for immunity in diphtheria is regarded at present as due to the direct irritant action of diphtheria toxin upon cells at the site of injection; if antitoxin is present in sufficient amount the toxin is neutralized and the inflammatory reaction does not occur. Trauma alone, the preservative, the interaction between protein constituents of the broth and non-specific ferments, or between the protein of autolyzed diphtheria bacilli and specific ferments, may induce a pseudo-reaction which may be mistaken for the true reaction.

It is probable that certain conditions accompanied by an increase of cells and their destruction, as in cancer and pregnancy, may result in the temporary increase of non-specific proteolytic ferments in body fluids and cells, and increase the tendency for the production of pseudo-reactions in the skin. As previously stated, there is also reason to believe that certain diseases accompanied by skin manifestations, as scarlet fever and other exanthemata, increase the tendency to skin reactions.

Summary.

1. Skin reactions may be (a) true or specific anaphylactic reactions; (b) pseudo- or non-specific protein reactions, and (c) traumatic reactions.

2. A non-specific or traumatic skin reaction may occur coincidently with, or be mistaken for, a true anaphylactic reaction.

3. Intracutaneous skin tests are more delicate than cutaneous tests, but also more likely to yield the non-specific and traumatic reactions.

4. The traumatic and non-specific protein skin reactions may be caused (a) by trauma and the direct injection of an irritant used as a preservative for the material, as phenol, or to a preformed toxic and irritant substance, as diphtheria toxin in the Schick test; (b) to the production of a protein poison of irritant qualities by the action of non-specific proteolytic ferments in the serum or derived from injured cells, upon the protein of the patient's serum, devitalized cells, injected protein, or all three.

5. The true anaphylactic skin reaction, however, is a specific process due to the interaction of specific anaphylactic antibody and specific anaphylactogen, largely within or upon the cells, and with the formation of a diffusible irritant similar to that produced in the non-specific reaction, capable of producing acute hyperemia, edema and leucocytic infiltration of the skin.

6. Certain drugs, as potassium iodide and potassium bromide, increase the non-specific reaction by facilitating the activity of non-specific proteolytic ferments and the production of protein poison, through the removal of anti-ferment; these drugs probably have no direct influence upon the specific anaphylactic reaction.

7. The specific anaphylactic skin reaction is acceptable as a delicate index of hypersensitiveness to a certain foreign protein or proteins, the enteral or parenteral administration of which may be expressed by various lesions and symptoms of disease.

8. The severity of a true anaphylactic skin reaction appears to be an index of the degree of hypersensitiveness.

9. A state of cutaneous anaphylaxis to a particular bacterial protein is not of itself an index of resistance or immunity to the living microparasite, although immunity principles may be coincidently present with the anaphylactic body.

10. At present the main clinical significance of the non-specific protein skin reaction is the likelihood of mistaking it for a true anaphylactic reaction.

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DISCUSSION.

DR. KRAUSE: I am sure that we all feel greatly indebted to Dr. Kolmer for coming here to-night and giving us this admirable summary of work that has been done in this extremely involved and difficult field of anaphylaxis.

I think that in any discussion of anaphylaxis we should keep in mind that no one has yet brought forward the proof that anaphylactic shock and the protein intoxication which manifests itself by symptoms that we generally call serum sickness are dependent on the same factors as the inflammation by which cutaneous hypersensitiveness expresses itself. I prefer to use the term anaphylaxis or anaphylactic shock to indicate the first condition, and cutaneous hypersensitiveness for the latter; and from the known facts at hand I cannot admit that the two reactions are the same, though in his paper Dr. Kolmer stated that it is generally agreed that they are identical.

Anyone who works in tuberculosis will soon learn that the conditions which will sensitize an animal in an anaphylactic sense will not necessarily sensitize its skin, and, that to bring about cutaneous hypersensitiveness, certain very definite and strict requirements must be fulfilled. It is the easiest thing in the world to sensitize a normal animal with tuberculo-protein so that subsequent intravenous or post-orbital injections of the protein will produce anaphylaxis. But an animal thus treated will not acquire skin hypersensitiveness. To attain this the animal must have a focus of infection (Römer, Baldwin, Hamburger, Krause). In no other way than by the introduction of bacilli and the consequent production of foci has anybody thus far succeeded in sensitizing an animal's skin. The mere parenteral injection of tuberculo-protein in any form—soluble or insoluble—will, however, render an animal anaphylactically sensitive.

After a number of years of work I could never determine that mere anaphylactic sensitiveness conferred any immunity upon an animal against bacillary invasion. An animal during the period of anaphylactic shock, and before it has completely recovered from the symptoms, will often strike one as being less resistant to infection. But in the period during which it is merely hypersensitive to protein, one can detect no alteration in its resistance.

The story is very different, however, once its skin (and other tissues) are hypersensitive. Skin (tissue) hypersensitiveness and immunity to infection (re-infection) occur under exactly the same conditions so far as we know: and it is not improbable that one is a function of the other. Skin or tissue hypersensitiveness expresses itself by the capacity of the skin or tissue to react in an inflammatory manner whenever the proper protein is applied *in situ*. The same inflammation will occur in the skin of a sensitive animal if the proper living bacilli are locally injected. We might therefore conceive that perhaps this inflammation occurring rapidly only in the sensitive animal after the implantation of living bacilli has a good deal to do in hemming in the bacilli and preventing their invasion of the organism. We might then consider that immunity to infection is in some way or other bound up in the inflammation by which a sensitive animal reacts.

As a matter of fact the tuberculous animal is both hypersensitive (skin or tissue) and immune. This hypersensitiveness and immunity both reach their maximum once a certain stage of activity of the disease is established. As the disease heals, both the hypersensitiveness and the immunity tend to diminish. Anaphylactic hypersensitiveness is not bound by these rules in tuberculosis.

It is not improbable too that the wide diversity of lesion met with in tuberculous involvement is largely determined by the variation in tissue hypersensitiveness at the particular time of bacillary implantation. The tuberculous pneumonias, the collateral inflammations, the œdema, the hæmorrhagic tissue reactions, the effusions into serous cavities are all expressions of local tissue hypersensitiveness produced by previous infection of the animal. I have never seen a normal animal react *immediately* to a first infection with tubercle bacilli in any other way than locally. But if the animal is already tuberculous, in other words, is already hypersensitive and relatively immune, then we shall find every kind of exudative or inflammatory reaction following re-infection: and the intensity and extent of the tissue alteration are determined by the degree of tissue hypersensitiveness on the one hand, and, on the other, by the number of bacilli brought to bear at any given point. In other words, the nature of the pathological change depends to a certain extent on the immune reactions of the tissues. I can think of no work that would promise more fruitful results than a rejuvenescence of the study of pathological anatomy in infectious disease, if the study were a comparative one and the diseases were studied developmentally. We should surely go far if we compared under natural and immune conditions the tissue response to irritation by micro-organisms, which, though related, are known to produce different effects.

TUBERCULOSIS OF THE TONGUE.

SPECIFIC CURE.

By Wm. Charles White, M. D., and C. Howard Marcy, M. D.

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An excellent paper on Tuberculosis of the Tongue by J. R. Scott[1] has recently appeared during the preparation of this report.

It is unnecessary to cover again the historical side of this field; reference to Dr. Scott's paper will answer every purpose in this regard.

A case has just come under our care presenting unusual features. The patient was under our constant supervision for advanced pulmonary tuberculosis for two years, prior to the advent of the lingual tuberculous ulcer which is reported here.

W. E., aged 30 years, applied at the hospital for care in June, 1914. At this time the family and personal histories were negative up to the time of his immediate illness, save for two attacks of pleurisy, one in 1906 and one in 1913. There was no remaining evidence of these attacks on physical examination during his stay in the hospital.

His tuberculosis had begun with cough and sputum three years before. His chief complaints on admission were cough, sputum, loss of weight, shortness of breath and sometimes pain on deep breathing. He had been at Mt. Alto, a state institution, without improvement, for six months prior to his admission to the Tuberculosis League Institution.

The physical examination on admission revealed signs of advanced tuberculosis of the lungs, involving both upper lobes completely and the lower lobes on both sides to the tip of the scapula. Cavitation was doubtful in the apex of the left lower lobe opposite the fourth and fifth dorsal spines. The sputum amounted to about 10 c. c. in 24 hours, and ranged in tubercle bacilli content from No. ii to No. vii (Gaffky). These were mostly long, slender, and beaded forms. His urine was normal, his Wassermann reaction negative. His blood examination: Hb., 90%; R. B. C., 5,800,000; W. B. C., 7800; diff. count: lymphocytes, 23.6%; large mono., 1.5%; trans., 3.40%; poly., 67%; eosinophiles, 3.5%; mast cells, 1%. His skin sensitiveness to O. T. was represented by no reaction to 1/100 c. c. of .25%, 1% and 2% solutions, but there was a positive reaction of 3 x 3 mm. to 1/100 c. c. of a 4% solution. On the basis of this reaction, he was given .00004 gm. of O. T.

FIG. 1.—Appearance of tuberculous ulcer of the tongue before treatment with tuberculin. This ulcer had persisted for six months.

FIG. 2.—Appearance of the same ulcer after four injections of .008 gm. O. T.

intradermally, in accordance with a method of dosage before described by us.[2] With this dose he gave an intracutaneous reaction of 2 x 2.5 cm. at the site of the injection dose. This dose was given for some time, then gradually increased in size over a period of 11 months, as he gained in weight and well-being. The sensitiveness had so far disappeared that on discharge, in May, 1915, he was receiving .009 gm. of O. T. In May, 1915, he was discharged and went home. He was greatly improved, having gained 17 pounds in weight and reached four hours' exercise (mainly walking) in 24 hours. He still had about 2 c. c. of sputum with a tubercle bacilli content represented by Gaffky ii. He took up light work, collecting and giving clerical assistance intermittently, as he could obtain it. He continued his tuberculin in the dosage last mentioned, and remained comparatively well till November, 1915.

In November, 1915, he noticed two small painless nodules developing on his tongue. These later broke down and developed an ulcer with a yellowish discharge. The chief symptoms of the ulcer were soreness and swelling. The pain was so severe when food was taken that the patient could not eat. He lost in five months 20 pounds. His home physician, Dr. Leydic, of Tarentum, treated the ulcer locally with silver nitrate and iodine for five months. In March, 1916, Dr. Leydic sent him again to the hospital. On admission, the lung lesion had not increased in area but was discharging more sputum. The whole amount was now 15 c. c. in 24 hours. The t. b. content was represented by Gaffky viii. The Wassermann reaction was negative. The blood examination showed: Hb., 90%; R. B. C., 6,470,000; W. B. C., 12,800; poly., 64.6%; lymphocytes, 28.2%; large mono., 6%; trans., 1.6%; eosinophiles, .6%. The high red blood cell count was probably due to his inability to take fluids, owing to the pain produced by swallowing and by taking into the mouth substances varying from the mouth temperature.

In addition an ulcer was found on the upper surface of the tongue 1.5 cm. in diameter, 2 cm. from the tip, confined to the right of the middle line. He was readmitted to the hospital.

Only by the use of cocaine locally was he able to eat. He lost 10 pounds in weight in two months in the hospital, and the ulcer continued to increase in size.

In April, Dr. Sieber removed a section of the ulcer. This was sectioned and examined by Dr. Bruecken and Dr. MacLachlan of the Department of Pathology of the University of Pittsburgh, and the diagnosis of tuberculous ulcer with giant cells and tubercle bacilli in the tissue was rendered.

The surgeon's advice was to excise the tongue wide of the lesion. In view of the fact that tuberculin had been given intradermally and had neither prevented nor cured the local infection in the tongue, its further use was considered as of no value. However, on account of some good results we had had with lupus, by injecting tuberculin into the base of the lupoid patch, we suggested that a trial be given to injection of tuberculin into the base of the lingual ulcer.

His skin sensitiveness was again taken, and his dose was found to be (by the method formerly described by us) .008 gm. of O. T. On May 4 this dose of old tuberculin was injected, from the side of the tongue, through the muscle substance, so as to infiltrate the base of the ulcer, with a long, fine hypodermic needle. At the end of 24 hours the tongue was swollen, red and a little more painful. At the end of 48 hours it was still slightly swollen, but not sore, and the increased redness was fading. After this the ulcer commenced to diminish in size, until at the end of one week it was not more than half the size and the patient was able to eat without pain.

On May 18 a second dose of O. T. was given in the same way, with a similar reaction and result, and one week later a reduction again of approximately 50% in the size of the ulcer.

On June 1 the same dose was given into the tongue. On June 2 he was discharged and returned to his home. On June 12 he returned again to the dispensary; at this time the ulcer had almost completely healed and he was again rapidly improving in weight and health. His last dose of tuberculin was given in July, when the ulcer was quite healed, and only a small fissure left to mark its former site.

Any explanation of the action of tuberculin in this case must be purely theoretical.

The patient had had far advanced tuberculosis of both lungs, which had healed with a large amount of fibrosis, and had left him afebrile and with a fair working ability. This may be taken as an indication of a great resistance, and that he had within his body somewhere, probably in his circulating fluids, substances which could be expressed in terms of tubercle bacillus resistance, if we had any means of isolating or measuring them.

On the one hand, there may be certain lytic substances in the circulating fluids in individuals who are improving from tuberculosis, but the structure of the tubercle devoid of blood-vessels may allow none of these to reach the central portion of the tubercle where the tubercle bacilli lie. The specific reaction to tuberculin, producing as it does a focal inflammation, may, by the accompanying swelling due to increased exudation, press apart the various cells packed around the individual tubercles and admit to the center of the tubercles any tubercle-bacilli-destroying substance present in the circulating fluids. This seems to us the most logical explanation.

On the other hand, it may be contended that all the inflammation does is to stimulate the production of mesoblastic cells at the periphery of the tubercle; that these later secrete fibrils which by contraction destroy the focus of the disease. The rapid cure which resulted in this case, after so long a persistence, makes the former contention more reasonable, as sufficient formation of new fibrous tissue could scarcely occur in four or five days after injection of the tuberculin to produce such reduction as occurred in the size of the ulcer. It is more likely that the diminution in size followed coincidently with the destruction of the etiological factor, that is, the tubercle bacilli.

If this procedure seems justified by further study, localized tuberculosis conditions can undoubtedly be very materially aided by this form of treatment. It seems especially applicable to local lesions in the laryngeal region and might safely be tried by those skilled in laryngoscopy.

It is not felt that we have reported any new procedure. The principle involved is probably the same which Dr. Trudeau found by specific treatment with tuberculin in curing tuberculous lesions in his rabbits' eyes.

Surely such a procedure is infinitely better in localized tuberculosis, such as the tongue lesion, than treatment by excision. The rapid cure after the long persistence in this case left no doubt about the influence of the specific agent.

NOTE.—Since this paper was written, the patient has returned with another tuberculous mass a little distance away from this in the tongue and this has been cured by two injections of tuberculin in a way similar to that described in this paper.

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ABSTRACTS OF PAPERS

Representing Work Done in The Johns Hopkins Hospital, but Published or to be Published Elsewhere than in the Bulletin. Prepared by the Authors.

DOUBLE URETER AND KIDNEY, WITH CALCULOUS PYONEPHROSIS OF ONE-HALF; CURE BY RESECTION. THE EMBRYOLOGY AND SURGERY OF DOUBLE URETER AND KIDNEY.

By HUGH H. YOUNG and EDWIN G. DAVIS.

(From the James Buchanan Brady Urological Institute, The Johns Hopkins Hospital, Baltimore.)

(Abstract from the Journal of Urology, 1917, I, 17.)

During recent years we have had in our clinic several cases of double kidney and ureter in which one portion of the double kidney was diseased. The present case is the only one of these which has come to operation, and is unique in that it is the only one of its kind to be found fully reported in the literature. The upper calculous pyonephrotic portion of a left double kidney with bifid ureter was diagnosed by means of pyelography, and the diseased portion was successfully resected, the lower normal portion being left *in situ* with an undisturbed blood supply and ureter. The patient, a man of 57, was admitted on April 7, 1916, to the James Buchanan Brady Urological Institute, complaining of a pain in the left flank. The pain was dull and aching in character, was increased by exertion; it had been present, with exacerbations and remissions, for 10 years. There was no history of any attack resembling renal colic. He complained also of frequency of urination, and the urinary examination showed a marked pyuria. The pyelogram showed on the left side a double renal pelvis with bifurcation of the ureter at the level of the third lumbar vertebra, and about 9 cm. below the lower pelvis. A large branching calculus completely filled the upper larger pelvis. There was no apparent abnormality of the right pyelogram. At operation (Young), a slight but distinct furrow was found demarcating the two kidney segments, and at this level it was possible to resect the upper portion, controlling a moderate amount of bleeding by mattress sutures through the upper pole of the normal portion. Convalescence was uneventful. The patient's symptoms (pain in the back and frequency of urination) were entirely relieved, and it was later demonstrated that the half kidney secreted normal, pus-free urine containing as much as 5 per cent phenolsulphonephthalein in one-half hour.

As to the embryology of bifid ureter, there is a general agreement among authors that this form of anomaly (bifid ureter or incomplete double ureter) may be accounted for by a premature or exaggerated bifurcation of the tip of the ureteral bud, the split extending varying distances down the ureteral stalk instead of being confined to the bulbous tip or primitive pelvis. This bifurcation normally takes place to a limited extent. The ureter first appears (in an embryo of about 5 mm.) as a budding or evagination from the Wolffian duct, close to the opening of the latter into the cloaca. The tip of the bud becomes bulbous as early as the 6.6 mm. stage, the primitive pelvis thus becoming differentiated from its more slender stalk, the future ureter, and as early as the 8 mm. stage a bifurcation of the primitive pelvis has taken place, separating it into upper and lower divisions, the first evidence of the calices. It may readily be understood that, if this normal bifurcation or splitting of the primitive pelvis should be excessive and extend down the ureteral stalk, two separate pelves and a bifid ureter would be produced. Felix describes this as a "precocious splitting of the ureter," the bifurcation taking place before the formation of the primitive renal pelvis, and the two ureters thus formed descending parallel to one another. He designates such forms of ureter as "cleft ureter," reserving the term "double ureter" only for those that have separate openings in the bladder. Complete double ureter is considered to be formed either as the result of two separate evaginations from the Wolffian duct, or as the result of the process of dilatation of the lower end of the Wolffian duct (and of the uncleft lower end of the ureter) by which the former comes to form a part of the bladder wall.

A complete survey of the literature shows that ureteral duplication is surprisingly common, especially in autopsy records, and occurs much more frequently than all the other forms of gross renal anomaly taken together. An average of the estimates of various observers places the frequency of this anomaly at about 3 per cent of all individuals. In the surgical literature, however, reports of bifid ureter and double kidney are quite rare. We were able to find only 26 case reports in which this form of anomalous kidney was explored surgically. In two of these the operation was undertaken merely on account of the incontinence produced by the supernumerary ureter opening externally (in the vagina), there being no lesion in the kidney itself, and in six cases the operation was nephrotomy. The remaining 20 operations upon double

kidneys were all nephrectomies, and in all but one (Albarran) the operation was complete nephrectomy. In the case reports of 16 of these nephrectomies it was definitely stated that half of the excised kidney was normal, and these 16 would therefore have afforded an opportunity for partial nephrectomy with preservation of a normal portion. Of the 20 nephrectomies the diagnosis of ureteral duplicity was made before operation in two instances only; in 18 the condition was accidentally discovered during the course of the operation, or later by an examination of the pathological specimen. There remains the case of Albarran, the only one in the series in which the normal portion of the kidney was preserved. Albarran, however, merely briefly mentioned his case in the transactions of the Association Française d'Urologie (1905), and has made no official report. It is of interest to note that, out of 24 cases of double kidney showing a pathological process in one segment, in 19 (practically 80 per cent) the upper segment was involved. In view of this uneven percentage it is fair to assume that partial obstruction of the superior ureter, due to its position with respect to the lower kidney segment and to the kidney pedicle, had been an important factor in producing disease.

CONCLUSIONS.

The case reported above is apparently unique in that it is the only such case to be found fully reported in the literature.

The condition of double kidney and ureter is not rare, and the upper half is most often the seat of disease; its surgical importance is therefore great.

The advent of ureteral catheterization, radiography and pyelography has made the diagnosis easy and we should expect the discovery of more cases in the future.

The radical cure by excision of the diseased half of the kidney with its pelvis and ureter is undoubtedly the method of choice.

THE EFFECT OF CALCIUM, WATER, AND OTHER SUBSTANCES GIVEN INTRAVENOUSLY, ON BLOOD COMPOSITION AND URINARY SECRETION.

By DAVID M. DAVIS.

(From the James Buchanan Brady Urological Institute, The Johns Hopkins Hospital, Baltimore.)

(Abstract of article in Journal of Urology, 1917, I, 113.)

In attempting to restudy the relation between blood composition and urinary secretion the effort has been made to inject quantities of fluid intravenously in such a way as to produce no diuresis. The changes in blood composition occurring under these conditions can then be determined.

Three procedures were utilized. In the first, distilled water; in the second, solutions of Ca, or of mixtures of Ca and Na chlorides; in the third, weak solutions of dextrose were injected.

It has long been known that distilled water given intravenously causes no diuresis. J. B. MacCallum concluded that calcium exercises an inhibitory effect on urinary secretion, though this has been denied by others. Woodyatt, by the use of an automatic pump, was able to prove that, if dextrose is given a dog at a rate of less than 0.85 gm. per-kilogram-hour, no glycosuria or diuresis occurs.

All the injections were made at constant rates over considerable periods of time, using a pump similar to Woodyatt's. Determinations were made while the injections were going on.

With distilled water, no diuresis was observed. The water content of the blood, however, increased 2 per cent, while the $\triangle$ of the blood fell 0.057°.

It was thought that Ca would probably decrease urinary secretion, since its biological actions are so generally antagonistic to those of Na. The observations of MacCallum were confirmed, the urine output being decreased. Where large doses of Ca solution were used, the hemoglobin percentage rose and the water content of the blood fell very markedly. The $\triangle$, however, remained constant, showing that a large quantity of isotonic fluid had gone to the tissues from the circulation. In other cases where Na was added to the Ca solutions and the amount of Ca reduced, the blood water content was less affected, showing slight increases, while $\triangle$ showed slight decreases. In these cases, the urinary secretion showed no, or slight, augmentation. A further experiment with kymograph record showed that these mixed Ca and Na solutions do not depress the general blood pressure.

When dextrose solutions were injected, at rates of 0.65 and 0.7 gm. per kilogram-hour, the blood water and blood sugar were increased, while $\triangle$ showed a moderate fall. One experiment showed diuresis during the second hour—evidently a subnormal tolerance.

Thompson, in an article published in 1900, has drawn conclusions concerning the mechanism of diuresis which there has been little reason to change since. According to him the diuresis, as measured by the quantity of urine secreted, does not run parallel to the blood pressure, the kidney volume, or the amount of hydremia.

Changes in the blood flow through the kidney have had ardent advocates for this important rôle. Löwi, using an extraordinary method, namely, the observation of the color of the venous blood as it emerged from the kidney, came to the conclusion that every diuresis is accompanied by an increased flow of blood. Such an inexact method does not invite great confidence, but Löwi is undoubtedly correct in supporting Thompson in his attack on the oncometric method as an index of blood flow in the kidney. Löwi enclosed the kidney in a plaster cast, making expansion impossible, yet with diuretics there was observed the change in color of the renal vein, to arterial red, that he associated with increased flow. Bunch demonstrated this in the most conclusive manner for the salivary gland, using an air plethysmograph and actually measuring the blood coming from the vein. Stimulation of the chorda tympani gave an increase in the blood flow with simultaneously increased secretion, but with a contraction of the gland. Histological studies of the kidney make it apparent that the renal epithelial cells vary greatly in size under different conditions.

It seems that one must conclude that diuresis can occur independently of changes in the blood flow. It is difficult to conceive how changes in the vascular bed, at most changes of 100 per cent or so, can cause increases in urinary secretion amounting to 10,000 per cent or more of the normal, if blood composition is constant or the changes in it are of no importance. In addition, changes in blood composition, as has been seen, do occur. The writer believes, therefore, that the burden of proof should rest on those who claim that blood composition is of less importance in diuresis than renal blood flow.

The older writers lay great stress on the concentration of the urine, especially in relation to that of the blood (Frey). It has, however, been demonstrated that the excretion of various substances reaches its maximum at a different time from that at which the diuresis is greatest, and from this viewpoint it is much more convenient to assume that each urinary constitutent, including water, has its own excretory mechanism, partially and probably in large degree independent of the others. The total molecular concentration of the urine would then be only an accidental resultant from the action of these mechanisms. It can then be further assumed with Magnus that an increase in the concentration of any constituent will cause its excretion in increased amount, and with Sollmann that the constituents of the blood provide the normal stimulus to renal activity. It is immediately apparent that the independence of the mechanism is not absolute, since one so seldom obtains a great increase in any constituent in the urine without a simultaneous increase in the water, although it is of course possible to do so, especially with certain constituents. Water occupies a peculiar position among urinary constituents, since its presence in the renal secretion is necessary not only to relieve the body of an excess, but also to act as a solvent for all the other constituents. It is suggested, therefore, that the mechanism by which so many salts produce a hydremia is a very necessary one for this purpose. It complicates the picture greatly, however, when explanations are attempted, especially since it makes the content of the body in water and other substances beforehand so important. That this has much influence on diuresis has been shown by Haake and Spiro.

But it is further suggested as an amplification of the theory of Magnus that, conversely, a decrease in the concentration of any urinary constituent in the blood tends to decrease renal activity and may serve to counteract the effect of a simultaneous increase in some other constituent. Thus, the simple addition of water to the blood would always bring about such a counteraction by simply diluting the blood, if not compensated in some way, and the bare statement that water given intravenously is not a diuretic scarcely affords an adequate explanation of the situation. Further, any procedure which caused any substance to leave the blood for the tissues would indirectly diminish urinary secretion.

It is felt that the experiments in this paper offer some support for this suggestion. The regulatory mechanism of the tissues is evident in the injection of hypotonic NaCl solution, where the chloride and molecular concentration of the blood is kept up to normal, while a hydremia develops, evidently at the expense of the colloid constituents of the plasma, and indicating, therefore, almost surely an increase in blood volume.

SUMMARY.

1. Injections of fluid in considerable amounts have been made intravenously in dogs, according to three methods, without producing diuresis.

2. In such cases definite hydremia and definite hyperglycemia may be present without diuresis.

3. Where hydremia occurs without diuresis, there has usually been a definite decrease in the molecular concentration of plasma, as shown by the depression of the freezing point ($\triangle$).

4. Solutions of calcium chloride given intravenously cause the urinary secretion to diminish, and in addition precipitate a great loss of water from the blood to the tissues. Given with sodium chloride, calcium chloride will antagonize the diuretic effect of sodium chloride. In such a case, the general blood pressure is not changed.

5. Various observations upon current theories of urinary secretion and additions thereto have been made.

A MODIFIED WOODYATT PUMP.

By D. M. Davis and W. S. Gorton.

(From the James Buchanan Brady Urological Institute, The Johns Hopkins Hospital, Baltimore.)

(Abstract from the Journal of Urology, 1917, I.)

The authors describe a simplified and less expensive form of an electric pump devised by Woodyatt. The mechanism actuates a Record syringe, and serves to make intravenous injections over long periods of time at predetermined and constant rates.

STUDIES ON THE GROWTH OF CELLS.

CULTIVATION OF BLADDER AND PROSTATIC TUMORS OUTSIDE THE BODY.

By Montrose T. Burrows, J. Edward Burns and Yoshio Suzuki.

(From the Departments of Pathology and the James Buchanan Brady Urological Institute, Department of Urology, The Johns Hopkins University, Baltimore, Md.)

(Abstract from the Journal of Urology, 1917, I. 3.)

Up to the present time no attempt has been made to cultivate bladder or prostatic tumors *in vitro*. Thinking that a study of this kind might aid in a better understanding of the clinical and pathological properties of these tumors, and that these tissues would possibly show peculiarities in their reactions which might aid in a better understanding of the growth of cells in general, we undertook this study.

Evidence had already been found which indicated that tissue cells were not highly organized elements. They are probably unable to utilize the food materials of the medium. Their growth depends upon the presence of specific substances. In the cultures these specific substances are liberated by the cells

within the fragment. A growth in the cultures is a simple transfer of materials from the cells within the fragment or, in a less favorable environment, to those on the periphery or those which migrate into the medium. Further growth in these cultures takes place only along surfaces. In many of the plasma cultures the cells grow along the surface of the fibrin. Measurements have shown that those cells which grow actively and divide by mitosis are not, however, directly in contact with the fibrin surface.

Human tissues liquefy the plasma clot, and the cellular activity is observed only in a small percentage of the culture. It is known that tissues of chick embryos and the embryos of several other animals, as well as certain malignant tumors, may grow in layers of liquid media, isotonic NaCl solution, Ringer's solution, serum, etc. In these media the cells grow in a plane near the free surface of the media or near the surface of the cover-glass over which the medium is spread. This has made it seem evident that the medium previous to the growth of the cells must have become covered with a layer of substance which was fluid in nature and had flowed out over the surface. In the cases where simple salt solutions were used as media, this substance must have come from the tissue fragment.

In the cultures of chick tissues it was often difficult to absolutely demonstrate the existence of such substances.

We have studied the culture of 12 tumors of the bladder and prostate. The method used consists in brief in placing small fragments of tumor tissue (1 mm. in diameter) in a layer of media (5 to 10 mm. in thickness) on the surface of a cover-glass, inverting over this a hollow ground slide, and sealing it in place with vaseline and paraffin. The cultures thus prepared were incubated at 37° C.

The media used have been prepared plasmata from the blood of patients from which the tumor was removed, plasmata from the blood of normal individuals and a medium consisting of agar, .25 per cent, dissolved in isotonic NaCl solution, or isotonic NaCl solution and acetic fluid. No difference was noted in the cellular activities of the cultures whether the plasma used as medium was obtained from the first or second source. The activity was as great in the agar medium as in the plasma.

Of the 12 tumors used for these cultures, seven were clinically malignant bladder papillomata; one was a benign bladder tumor, two were cases of benign hypertrophy of the prostate and two were prostatic tumors, each of which showed in one portion typically benign hypertrophy, the other part having undergone carcinomatous change. Besides these, one series of normal bladder epithelium was also tested. Cellular activity was observed about the fragments of all of the malignant tumors excepting two. One, a bladder tumor, which had been removed after an application of a strong solution of cocaine, and the other, a malignant cancer of the prostate, which had been treated for four months with radium. No cellular activity was noted about the fragments of normal bladder epithelium, about any of the fragments of the benign tumors, or the benign portions of those prostatic tumors which showed local areas of carcinomatous change.

The plasma clots were liquefied around all the fragments of tissue studied. This was not only true of the first culture, but it occurred again if the fragments were transplanted to fresh plasma medium after 24 hours. The cellular activity took place in a liquid medium. In these cultures it was possible to see a membrane form over the surface of a medium. It formed always previous to the growth of the cell. No membranes formed about the fragments of normal epithelium, or the fragments of the benign tumors. The membranes that formed about the fragments of malignant tumors contained a large number of granules which made them easily seen. A sharp line of demarcation between them and the underlying medium was not made out. The surface of the medium which they covered was held fixed and could not be disturbed easily by shaking. The cells migrated in a plane just beneath this membrane.

These observations have shown several facts of interest: First, that the diffusion of a substance, or certain substances, from the tissue fragment over the surface of the medium to form a membrane was essential for the activity of the cells; second, the cells move in contact with the surface of this membrane; third, that such a diffusion and cellular activity are observed only about the fragments of the definitely malignant tumor; fourth, there was no diffusion of such substances or cellular activity noted demonstrable about the fragments of one of the malignant tumors which had been treated for four months previously with radium. These last facts indicate that this method may be important in determining the malignancy, following the course of treatment and studying the biological properties of these tumors.

THE RELATION OF THE NON-PROTEIN NITROGEN TO THE UREA NITROGEN OF THE BLOOD.

By HERMAN O. MOSENTHAL and ALMA HILLER.

(*From the Medical Clinic of The Johns Hopkins Hospital.*)

(Abstract of article appearing in the Journal of Urology, 1917, I, 75.)

Considering all the cases studied, it is apparent that as the non-protein nitrogen of the blood rises it is accompanied by a disproportionately rapid increase in the urea. This is expressed in the upward trend of the percentage figures for the urea nitrogen of the total non-protein nitrogen.

The conclusions which may be drawn from a closer analysis of these statistics are as follows:

In chronic nephritis, not complicated by myocardial insufficiency or uremia, the relation of the urea nitrogen to the total non-protein nitrogen of the blood shows that the urea increases faster than the non-protein nitrogen, the increase being very similar to that which is found when all the cases are averaged, and presenting no special characteristics.

In cases of nephritis complicated by uremia, the percentage of urea nitrogen has a tendency to be higher than in any other class of cases. Especially noteworthy is the value of 75 to 80 per cent in cases in which the non-protein nitrogen of the blood is 40 mg. per 100 c. c. or less.

Cases of myocardial insufficiency show a marked rise in the percentage of urea nitrogen in those rather rare instances when the non-protein nitrogen increases in the blood beyond the normal of 30 mg. per 100 c. c.

Patients suffering with chronic nephritis complicated by myocardial insufficiency accumulate urea more rapidly in proportion to the other non-protein nitrogenous constituents of the blood than do the cases of chronic nephritis not associated with myocardial insufficiency.

Cases with acute nephritis exhibit a decidedly higher percentage of urea nitrogen than do the instances of chronic nephritis.

The cases with a high non-protein nitrogen in the blood, not included in the previous groups, have a lower proportion of urea nitrogen to the total non-protein nitrogen of the blood than those afflicted with uremia, and they approximate the figures given for chronic nephritis.

Many patients with a normal total non-protein nitrogen of the blood—that is, less than 30 mg. per 100 c. c., show a higher proportion of urea nitrogen than the normal of 50 per cent, though their clinical condition would indicate no renal involvement. The proportionately higher quantity of urea found in the blood of these individuals is believed to demonstrate a depression of renal function.

In acute renal disease, followed by improvement, the percentage of urea nitrogen in the blood may rise and again return to the normal of 50 per cent or less, thus reflecting the progress of the condition.

The relation of the urea nitrogen to the total non-protein nitrogen exhibits a tendency to remain unchanged in each patient. Thus, three cases of chronic nephritis over considerable periods showed a fairly constant concentration of urea nitrogen at a normal level of 50 per cent or less, at a level of 65 per cent, and at 70 to 80 per cent, respectively. This moderate fixation is not to be accounted for by unvarying values of the total non-protein nitrogen, for in each patient these fluctuated widely. The protein katabolism and anabolism may result in exceedingly marked loss or retention of nitrogen, which at times may be reflected in the level of the total non-protein nitrogen and urea nitrogen of the blood, at others, not; in spite of this, the percentage of urea nitrogen remains fairly constant.

It is tempting to assume that the metabolic activities of the tissues through increased protein breakdown may also be responsible for part of the picture. However, when cases are examined in which there is retention of nitrogen due to renal insufficiency alone, not complicated by changes in the other tissues of the body, the same high percentage of urea nitrogen is demonstrated. Polycystic disease of the kidney represents such a condition. In this disease, the same increase in the percentage of the urea nitrogen in the blood as in the instances of nephritis was demonstrated. After nephrectomy in a dog, which may be regarded as an example of maximal uncomplicated renal insufficiency, the percentage of urea nitrogen rapidly rose as high as 86 per cent, and remained in this neighborhood until death supervened.

Taking these facts into consideration, it would seem that ordinarily when protein material is metabolized, approximately 80 per cent of the nitrogen passes into the blood in the form of urea, which is the percentage of urea nitrogen found in the normal urine. Kidneys whose function is not involved maintain the percentage of urea nitrogen of the total non-protein nitrogen at a level of 50 per cent or less in the blood. As the kidneys become inefficient, their impairment of function is recorded in a rise of the percentage of urea nitrogen.

STUDIES ON THE METABOLISM OF CELLS IN VITRO.

I. THE TOXICITY OF α-AMINO-ACIDS FOR EMBRYONIC CHICKEN CELLS.

By Montrose T. Burrows and Clarence A. Neymann.

(From the Pathological Laboratory and the Laboratory of Internal Medicine, Henry Phipps Psychiatric Clinic, The Johns Hopkins University, Baltimore, Md.)

(Abstract from Journal Exp. Med., Jan. 1, 1917, XXV, No. 1, pp. 93-108.)

The observations recorded were noted during a series of studies directed towards finding an artificial medium for cultivating cells *in vitro*. In the tissue culture the nutrient materials for the growing cells are derived from the cells disintegrating in the center of the fragment of tissue. The culture reaction is none other than a transfer of material from these cells in a less favorable environment to the growing cells on the periphery of the fragment which are in a more favorable environment. Previous evidence had given rise to the belief that the body cells are fluid-like structures. In the cultures they are unable to break down complex substances and to build the products thus liberated into their own protoplasm. Cell growth is a reaction between the cell and a specifically organized mechanical and chemical environment. It is a differential surface tension reaction. There is a definite period for the growth of cells about a given fragment which has been placed in a medium of blood plasma. Transplanting the fragments every three days, we can thus predict the number of transplants in which growth will take place before the cells become exhausted. The number of transplants differ with different tissues.

We observed the effect on the cells of the addition of carbohydrates, fats, peptones and α-amino-acids to the medium. Fragments of heart muscle and skin of chick embryos and fœtal chickens were the tissues used. They were planted in plasma, prepared from the blood of adult chicken. The addition of carbohydrates and fats caused no change in the growth activity, which is of present interest. The addition of a 2.5 per cent isotonic solution of peptones prepared from the yolk of eggs did not in any way effect the growth. The addition of an isotonic solution of a mixture of α-amino-acids, prepared by hydrolizing egg yolk proved toxic. Fearing this toxicity might be due to the method of preparation, we tried the addition of isotonic solutions of the individual α-amino-acids. These also proved to be toxic when used in certain concentrations. The cells of young embryos were killed after

a few days' growth in the first culture. The cells of the older embryos and fœtal chickens were more resistant, but they were also killed after a few transplants. Lower dilutions inhibited the growth and eventually killed. At first, however, they showed slight stimulation. This was a functional rather than a growth stimulation; it was seen only in those cultures in which fragments of heart muscle had been used. This stimulation was noted by the active contraction of the fragments.

FURTHER OBSERVATIONS ON THE USE OF THORIUM IN PYELOGRAPHY.

By J. EDWARD BURNS.

(From the James Buchanan Brady Urological Institute, The Johns Hopkins Hospital, Baltimore, Md.)

(Abstract from the Journal of the American Medical Association, 1917, LXVIII, 533.)

Since the publication of the preliminary report on the use of thorium solution as a pyelographic agent, many experimental investigations as to its pharmacologic action and much clinical evidence after its employment in 185 cases have led to the conclusion that it fulfills all the conditions requisite for an ideal pyelographic medium. It is non-toxic (within the ordinary limits of usage), non-irritating, opaque to the Roentgen Ray, giving a splendid outline of renal pelvis and ureter and is inexpensive, being about one-third the cost of collargol. The solution contains the double citrate of thorium and sodium, sodium citrate and sodium nitrate. It is a clear, watery solution (therefore perfectly clean) which is not bactericidal, and should therefore be sterilized before being used. For pyelograms, the 15 per cent solution should be used, and for cystograms the 10 per cent solution. The gravity method should always be employed in the introduction of the solution into the renal pelvis and ureter. Great care should be exercised in making pyelograms in cases where there is marked impairment of renal function, for in such cases the introduction of any solution into the renal pelvis might so disturb the already markedly impaired functional activity of the kidneys as to cause the onset of uremia. This solution, either by its adhesive properties, by its capability of being absorbed, or by means of its comparative density, accentuates the shadows of calculi in the urinary tract when they are not ordinarily seen in the plain roentgenogram.

NOTES ON NEW BOOKS.

Diseases of the Eye. By GEORGE E. DE SCHWEINITZ. Eighth edition. Cloth, $6.00. *(Philadelphia: W. B. Saunders Company, 1916.)*

It is a common weakness in the writings of men who have had their training along ultra-pathological lines that the element of practical application is obscured by the ætiological, histological and allied considerations. Fuchs' inestimable text-book has been rendered as practical as it is because of Alexander Duane's parenthetically inserted notes.

Similarly, in the earlier editions of de Schweinitz' book, the minutiæ of the therapeutic sections were lacking, and the practitioner, seeking to apply the outlined treatment to a given case, could not always find, in the text, the proportions of the suggested remedies.

Furthermore, the section on extraocular muscles and the orthoptic, gymnastic procedures variously employed for derangements in them were also slighted in the earlier volume. On these grounds one ophthalmologist, having felt this to be a great drawback, has criticised de Schweinitz' work somewhat severely.

The more recent editions have been gradually perfected, and we have, in the last revision, a work truly comparable with Fuchs' production, and, certainly, the leading ophthalmological text-book in the English language.

With the incalculable advantage of an early start in his writings de Schweinitz has been able to review his own work repeatedly, while still in the heyday of his active career; and because of these revisions the book is thoroughly up to date in every particular and is one which can, with safety and profit, be used as a guide by the practitioner.

The most important addition to this eighth volume is the perimetric work of Clifford Walker, whose visual field studies are now classic. The consideration given these investigations proves that the broadest and most important line of oculistic endeavor, at the present time, is perimetry which, with ophthalmoscopy, as now being worked out, is recognized as the greatest and surest connecting link between ophthalmology and its parental subjects—medicine and surgery.

The section on operations is most complete. If any ophthalmic volume is ever to become as standard as Fuchs' text-book, this of de Schweinitz will be the one. L. W.

The Principles of Diagnosis and Treatment in Heart Affections. By SIR JAMES MACKENZIE, M. D. Cloth, $2.50. *(London, Oxford University Press: Henry Froude and Hodder & Stoughton, 1916.)*

Based upon the conspicuous ability for observation and careful study which has been emphasized by the surmounting of unusual obstacles to research, an almost holy reverence has grown up for the work of Sir James Mackenzie. It is, then, a little disappointing that he should have thrown together a few rather elementary lectures and philosophical comments on cardiac conditions and should have published them. From the great much is expected, and the title of this book had rather forecast a summary and conclusion of his life's work that would endure as his monument to future generations.

In reviewing the book, there are, in addition to the short and numerous notes from his rich experience that must be dug from the text, several points that merit careful consideration. In the first place, heart failure or myocardial insufficiency, as it is often designated, represents the inability of the heart to play its demanded part in the physical life of the individual. The particular lesion and its characteristic physical signs are only secondarily important. Again, clinical signs, unfortunately, fall down where cardiac efficiency is questioned; hence the need for more careful histories and more exact study of symptoms, which are, after all, the earliest signs of heart failure. Further, the knowledge of the wound is emphasized—the variance of its characteristics in different ages and under different conditions—and the fact that the diseased heart represents a physiological response to a pathological demand is stressed. And in diagnosis this book points out the impossibility, as a rule, of relying on any one sign to supply the sole basis for our conclusions.

From the patient's point of view, Sir James Mackenzie brings out the importance of prognosis. He speaks against the present

unfortunate relationship existing between the hospital and dispensary method of treating cardiac cases, in which the most experienced practitioner devotes his time to the clever but useless diagnosis in the ward of relatively incurable conditions, while the incipient and often more or less curable cases are left to a rushed and more inexperienced dispensary physician.

Above all, this book brings to the attention of the general practitioner the unique position he occupies in clinical research, in being able to study the course of cardiac cases, the progress and prognosis to be drawn from individual symptoms and signs, and their response to treatment. E. W. B.

Instinct and Intelligence. By N. C. Macnamara, F. R. C. S. 8 vo, 216 pages. Cloth, $2.00. (*New York: Oxford University Press, 1915.*)

The author endeavors "to give an outline of the evidence and the reasons upon which we rely to prove that the instinctive behavior of human beings depends on work performed by definite parts of the brain; consequently, education has not only to deal with the training of something immaterial which we call mind or consciousness, but has first and foremost to deal with the proper development of the nervous substance of that part of the brain, the orderly working of which is essential for the occurrence of instinctive and intellectual phenomena. In the majority of healthy children this purpose can be attained by means of the appropriate exercise of their eyes, ears, and other sensory organs; for, as we explain, energy derived from this source stimulates and develops the living substance of those parts of the brain directly concerned in the elaboration of an individual's instinctive and intellectual processes; we may thus hope to lay the foundation on which to build up a chaste, self-reliant character, combined with a clear and strong intellectual capacity."

In the main there is rather more effort spent on the consideration of the neural corollaries than on the concrete instincts and our means of forging them into intellectually controlled power. The discursive rather than intensive type of discussion of the above point of view brings together many interesting, though mostly elementary, facts for a beginner or for an hour of leisure.

The Priniciples and Practice of Perimetry. By Luther C. Peter, M. D., F. A. C. S. Cloth, $2.50. (*Philadelphia: Lea & Febiger, 1916.*)

In this fascinating little book of two hundred pages, the author has not only compiled all that we have, or ought to have, read on the subject and added personal observations of great value, but has, in addition, breathed into the dry facts thus gleaned the warmth and enthusiasm of a man thoroughly engrossed in his subject.

Besides a most complete bibliography, introduction and appendix, we find a table of contents which is arranged in a group and sub-group system, making the book invaluable for quick reference to one familiar with the general subject and desirous of omitting unnecessary details. The text throughout is profusely illuminated with instructive diagrams and charts.

Perimetry is a most difficult subject to handle with any degree of dogmatism, because of the varied interpretations which may be put upon the same findings depending upon associated states. It is due to this, no doubt, that no English-speaking physician has ever before attempted a volume on this special branch of ophthalmology. For this reason, as the author says: "Dovetailing of the practical and the academic has been found to be the logical method of presenting the subject."

Dr. Peter makes a good point with which many observers will agree. He contends that most color-field averages given in the text-books are too high for the normal encountered in practice; the expressed desire for an iron-clad standardization of colors must meet with uniform approval, it being well appreciated, for example, that a deep orange-red will give a larger field than a true red.

His statement, however, that in man overlapping of the visual fields reaches its highest degree, will not be accepted by some of his readers.

Another item of practical import is that the taking of fields is a matter of training to the most literate patient, the first records not being dependable and that for the sake of accuracy several remeasurements are necessary.

To oculists who deplore the careless field-taking of most surgeons, it is refreshing to see emphasis laid upon the size of the blind spot and the zone of impaired color sensation about it.

The reviewer, personally, does not agree with the author's grounds for his preference for the daylight illuminated perimeter over the electrically transilluminated instrument, because the former varies with bright or cloudy days, and the time of the day, as well as the direction of the light, whereas the latter, used in a dark room, is standard and invariable. As to the advantages of the campimeter over other scotometric devices, we are fully in accord with the author's views.

The classification of scotomata is excellent, and could profitably be accepted as standard. It is interesting to note that Peter disputes van der Hoeve's "ring of indistinct scotoma" surround the normal blind spot, and contends that its presence is the first sign of enlargement of the latter.

The value, in diagnosis and prognosis, of perimetry, frequently practised during the course of regressive processes in intraocular disorders, is clearly demonstrated.

The whole perimetric subject is brought under two heads: (a) General pathology of the visual fields. (b) Special pathology of the visual fields. Details are given and the visual tract is divided into groups for systematic study and isolation.

The reader is astonished at the very evident thoroughness with which the author has examined the visual fields of cases embracing, apparently, almost every condition which would show any perimetric change whatever.

An individual point not emphasized elsewhere in literature, so far as the reviewer is aware, is the presence of an indistinct, scotomatous area in the prescotomatous stage, or immediately surrounding a definite scotoma—a region in which color and form are determined, but with great uncertainty.

One of the most striking sections of the book is the one containing the assertion that reversal of the color fields in choked disk is psychic in origin, and not organic, and pointing out the fact that neoplasms in various parts of the brain may produce such a reversal.

The objection that, if Cushing's and Walker's explanation that nasal contraction of the visual fields in brain tumor with choked disk is due to pressure of the chiasm outward against the carotid arteries by the distended third ventricle is an acceptable hypothesis, there should be altitudinal changes as well, because the same force would crowd the chiasm down upon its bony bed in the sphenoid, is well taken. Peter's explanation of the phenomenon on other grounds is well worth consideration. He says that, because of the eccentric location of the disk, and the fact that "the temporal distribution of the optic nerve is accomplished by a longer and more circuitous route than the direct radiations of the nasal retina," he regards the nasal contraction as a purely intraocular affair such as occurs in glaucomatous atrophy. He quotes Siemerling's case for proof of the pathological contention that distention of the third ventricle would be more apt to produce bitemporal than binasal hemianopsia.

There is a splendid summing up of the various changes in glaucomatous fields with points on perimetric diagnosis.

In diseases of the optic nerve proper, the visual field changes characteristic of the various forms of posterior sinus disease are

clearly demonstrated and lucidly explained, the findings of Markbreiter and others, who have recently conducted classical investigations into this particular branch of perimetry, being carefully tabulated for the rhinologist's benefit.

In discussing toxic amblyopia, it is interesting to note that Peter gives some preference to the less popular theory that the process begins in the ganglionic cells of the retina, secondarily spreading to the nerve fibres or papillo-macular bundle and not conversely.

There is an excellent section on fields in disease of the chiasm, with the various views as to the *modus operandi*, richly illustrated with charts. Under this heading, Peter warns against the bizarre and heterogeneous fields of organic chiasmal disease frequently complicated by hysteria, with the consequent double and misleading perimetric findings.

Under diseases of the optic tracts, the author agrees with Hess and Walker that the Wernicke pupillary phenomenon and the Wilbrand prism phenomenon are of no value in localization of a lesion in, or anterior to, the basal nuclei from one above these nuclei in the optic radiations and cortex. But he believes that, if the technic is perfected to more scientific precision, the former test may be of value in locating the seat of the lesion in hemianopic central amblyopia.

The section on diseases of the optic radiations is really fascinating, and of great interest to the neurologist as well as the ophthalmologist.

The best section of the book, however, is Part IV—Fields in Functional Nervous Diseases—wherein all the latest studies are collaborated and presented in such a systematic form that it will prove invaluable as a supplement to the studies of the neurologist or internist in the difficult differential diagnoses so often confronting them.

Altogether, this little volume is one well worth having, and grows upon one with each reading.

It is to be hoped, however, now that the first edition has been received so well, that Dr. Peter will soon present the subject in still greater detail and technicality, for it is one of unending possibilities. L. B. W.

Physical Diagnosis. By JOHN C. DA COSTA, JR., M. D. 3d edition. Cloth, $3.50. (*Philadelphia and London: W. B. Saunders Company, 1915.*)

The subject matter, arranged as in preceding editions, has been somewhat enlarged. The illustrations are good and original. The topographical charts add much to the clearness of the text. The pathology of diseased conditions is briefly treated along with descriptions of the physical findings. Diagnosis by means of the electrocardiograph, the sphygmomanometer and the X-Ray is discussed and examples are given in their proper places. This should prove a very useful book. M. A. H.

Obstetrics, Normal and Operative. By GEORGE PEASLEE SHEARS, M. D. Cloth, $6.00. (*Philadelphia: J. B. Lippincott Company, 1916.*)

This recent addition to the rapidly growing number of text-books of obstetrics is an attempt, as the author says in the preface, to eliminate the irrelevant matter usually present in such works and to give more attention to the practice of obstetrics. The result is a one-man book with many glaring inaccuracies and omissions. There is throughout the work an evident lack of familiarity with the recent scientific literature. The author in large part relies upon his own personal experience, but does not substantiate his assertions with any actual figures. There are numerous unnecessary repetitions and cross-references that tend to annoy the reader and distract his attention.

As examples of the inaccuracies might be cited the reference to obstetrician as a word of Greek derivation, the statement that the urea and ammonia determination require two or three days' work, that syphilis is the most common cause of abortion, that occiput posterior positions are usually associated with disproportion, that the blood loss in a normal labor is 80-100 gm., that rickets is hereditary and so on. In speaking of acute yellow atrophy of the liver it is stated that it occurs so frequently among pregnant women that it was called "icterus gravis" by the older writers.

Several practical points are entirely omitted: rectal examinations during labor are not mentioned, nor is tamponing the uterus after delivery in cases of placenta prævia; manual rotation of the head before applying forceps is scarcely considered. Delivery of the head by the Ritgen maneuver or some modification of it is not included in the discussion of a normal delivery. Chronic nephritis is treated separately from the other toxemias and, in spite of its frequency and the excellent results obtained by reasonably intelligent treatment, the entire discussion is contained in 22 lines and the only treatment mentioned is the termination of the pregnancy. On the other hand, asphyxia neonatorum is given 22 pages and 14 large illustrations, five of which picture the Sylvester and Schultze methods, neither of which has anything to recommend it in the treatment of this condition.

The author's chemical views are put forth in such a manner as to be very confusing. Sub-oxidation, a very indefinite term, is used to explain the manifold metabolic disturbances of pregnancy and a theory of the cause of eclampsia is based upon this unproven deprivation of the tissues of oxygen. In fact the lack of oxygen is blamed for many things and the therapeutic use of the gas is recommended in almost every condition for the mother and child. The observation upon the fetal heart rate when the mother is given oxygen by inhalation is so opposed to current physiological opinion that it needs to be confirmed by some more exact procedure before being accepted as an exception to the usual result of increasing the oxygen supply.

In general the advice given is sound and in conformity with modern conservative prevention and therapy; but occasional dangerous bits of teaching are noted. It is stated that 2½ or 3 hours' first-stage pains without progress supply an indication for forceps and the author further states that when a patient says she "can bear it no longer" she should be delivered instrumentally. It is truly pernicious to propagate such views among the physicians of the country who are already far too radical in their use of artificial methods of delivery.

The illustrations are mostly quite familiar and practically the only original ones are reproductions of photographs which, although exemplifying the photographer's art, do not rank very high in the realm of medical illustration. E. D. P.

Diseases of the Skin. By HENRY H. HAZEN, M. D. Cloth, $4.00. (*St. Louis: C. V. Mosby Company, 1915.*)

It is true, as the author states in his preface, that an apology is needed for adding another text-book on diseases of the skin to the many now available. But if an author can demonstrate good reasons for his work, such as a departure from the usual methods of treating his subject—in other words, if he shows originality or the emphasizing of important aspects—we are obligated at least to become acquainted with his presentation. Dr. Hazen, writing especially for students and practitioners, has departed from the usual text-book methods in several ways. He has given a classification of diseases for the most part based on etiologic or pathologic, rather than on anatomic, grounds; moreover he has emphasized the pathologic and histo-pathologic aspects especially of the commoner diseases—a factor which we believe to be of the highest importance for the teacher and of the greatest significance for the pupil.

We welcome particularly the chapters on etiology, symptomatology, diagnosis, treatment and hygiene as concise yet fairly com-

plete presentations of the most important aspects of study of the various dermatoses. A text-book of this size and purpose must of necessity be so brief that the author is constrained to become rather dogmatic in his statements. We must, therefore, accept with a certain amount of reserve various statements made in the section on etiology. The discussion on symptomatology is good, especially on that of occupational diseases.

The methods recommended for diagnosis are based, as the author states, on the splendid little system arranged by Dr. Gilchrist for use in his teaching in The Johns Hopkins University courses. The author uses a modification of this, which means that the disease is diagnosed by a consideration of the primary lesion, the arrangement and distribution of lesions, the objective symptoms etc., the system being used very much as a key similar to that in a text-book on botany or the like.

The chapters on therapy and hygiene are sufficiently complete for a book of this size. We are pleased to note that sufficient space is given to X-Ray therapy which has won for itself, in recent years, such an important place in the alleviation of skin disorders. A very brief account only is given of radium, and too little of electrolysis—two very important agents in the therapeutic armamentarium. The sections on hygiene and on professional and trade dermatoses are clear, brief, and very practical.

We are pleased to note many excellent prescriptions which are written in the metric as well as in the usual system; but some of these require correction and would be more instructive were they written out in full, especially for the student who is frequently not too well equipped in this important part of medical training.

There are a few points of minor importance to which attention may be directed, such as the use of the term "barber's itch" as a synonym for two different diseases; namely, sycosis vulgaris and sycosis parasitica. In the section on tuberculosis of the skin (lupus vulgaris) the author makes no mention of the importance of a generalized or a pulmonary tuberculosis as a probable accompaniment of the disease of the skin.

In a brief review such as this it would be difficult to discuss every section; but attention should be called especially to the excellent sections on eczema and on syphilis.

It is unfortunate that nearly every photomicrograph is practically worthless because the histologic changes are so poorly depicted. But too much praise cannot be given for the excellent photographs, most of which we know, from personal association, have been made by the author and his teacher and associate, Dr. Gilchrist. A good photographic representation of a disease of the skin is the most eloquent kind of description and the most lasting for the student mind.

Like many books of its kind it is up to date, especially in the adequate summaries of many of the rare diseases. It has the advantage that the author always gives an account of his own experiences and work in dermatologic fields—which, if not always in accord with the usual opinions of other and older dermatologists, at least makes the book individual. In this connection, also, the book expresses, as the author states in his preface, many of the views and some of the therapeutic measures adopted by the dermatologic staff of The Johns Hopkins Hospital. Furthermore, the author has taken pains to give his findings in studies of skin diseases in the negro, which are always instructive and interesting, at least by way of comparison.

The book is attractively bound, is very handy, and when proper correction is made of the occasional typographical errors, it can well make a claim for use as a text-book for the student, who has not the time to read the more comprehensive works, and for the practitioner who is too busy to delve too far into the possibilities of a puzzling diagnosis. I. R. P.

Skin Cancer. By Henry H. Hazen, M. D. Cloth, $3.00. (*St. Louis: C. V. Mosby Company, 1916.*)

This is a book primarily for the clinician and deals not only with skin cancer and cancerous lesions but also with skin lesions which might be mistaken for cancer. The description of cause and symptoms is brief but complete. The subject of differential diagnosis is well summarized in a separate chapter. In addition to this there is an excellent chapter dealing with treatment in a way which is neither too radical nor too conservative. The book is well arranged and very readable. It offers an excellent résumé of the subject of cancer of the skin. It cannot be too highly recommended to the profession, for it is a thoroughly modern treatise. J. C. L.

Blood-Pressure, from the Clinical Standpoint. By Francis Ashley Faught, M. D. Second edition. Cloth, $3.25. (*Philadelphia: W. B. Saunders Company, 1916.*)

The practitioner will find in this book a complete and well-balanced summary of the ponderous literature of late years upon this important subject. The whole is tempered by the author's good scientific insight and conservative clinical judgment. In the preface the writer begs latitude from the strictly scientific investigator for his attempt to draw clinical conclusions from laboratory data, but one is rather struck by the absence of the attempt to elaborate his own hypotheses without a substantial background of fact.

The text is introduced by a review of the physiology of the circulation and of the factors concerned in the maintenance of blood-pressure. The various methods for estimating blood-pressure are discussed and the instruments to be used are described, under their market names, in detail. The blood-pressure in health and the effect upon it of various external factors—race, climate, altitude, age etc., are also dealt with.

Then follows the clinical application and the subject of blood-pressure is correllated with the following conditions—acute infections (with sub-headings), arteriosclerosis, nephritis, cardiac disease, surgical operations and obstetrics and in its relation to life insurance. There is an appendix upon the therapeusis of hypertension.

The book does not mark an epoch in the study of blood-pressure, but, with a few very minor exceptions, it is a careful compilation of our knowledge, to date, of this subject.

J. T. K., Jr.

International Clinics. A Quarterly of Illustrated Lectures and Especially Prepared Original Articles. Vol. III. Twenty-sixth series. Cloth. (*Philadelphia and London: J. B. Lippincott Company, 1916.*)

Any comment upon this work would be entirely superfluous. The name is all that is necessary to recommend the perusal of its contents. Of especial importance in this volume is the consideration of pneumothorax and tuberculosis, both from a clinical and roentgenological standpoint.

Urgent Surgery. By Felix Lejars, translated from the seventh French edition by Wm. S. Dickie, F. R. C. S. Vol. 1. Cloth, $7.00. (*New York: William Wood & Co., 1914.*)

This book offers very little to recommend itself under such a title. It is extremely redundant, both in writing and illustrations. It is written in the first person and the present tense and becomes tiresome reading. The subjects are handled in a scattered, diffuse manner and one gains a very poor impression of what one should do in cases of urgent surgery. In short, there is nothing in this book, that is not found in any of the minor text-books of surgery, where the subject will be found presented in a very much more logical and succinct manner.

Cerebellar Abscess, Its Etiology, Pathology, Diagnosis and Treatment. By ISIDORE FRIESNER, M. D., and ALFRED BRAUN, M. D., F. A. C. S. Cloth, $2.50. (*New York: Paul B. Hoeber, 1916.*)

This is a very comprehensive and excellent treatise on abscess of the cerebellum. As an introduction, there is a very good consideration of the anatomy and physiology of the cerebellum. The etiology, pathology, symptoms, prognosis and treatment are separately and quite thoroughly considered. There is a very good bibliography.

Practical Bandaging, Including Adhesive and Plaster-of-Paris Dressings. By ELDRIDGE L. ELIASON, A. B., M. D. Cloth, $1.50. (*Philadelphia and London: J. B. Lippincott Company, 1914.*)

This is a small book giving illustrations of the bandages most commonly used. There is nothing especially new, the bandages being mostly of the type found in all text-books. Many of the newer bandages that possess more or less individuality are not included. The book, however, is very well condensed and should be useful for the medical student.

Studies in Surgical Pathological Physiology from the Laboratory of Surgical Research. New York University. Vol. I. Cloth. (*New York University, 1915.*)

The value of this work lies in the stimulus for experimental observation in surgical laboratories. It includes quite a fund of experimental work bearing upon practical problems. The papers are presented in their original form, as the subjects are so diffuse as not to allow their arrangement in any systematic grouping. The caliber of the articles necessarily varies, but most of them will be found valuable by those engaged in experimental work.

Bone Graft Surgery. By FRED H. ALBEE, A. B., M. D., F. A. C. S. Cloth, $6.00. (*Philadelphia and London: W. B. Saunders Company, 1915.*)

Because of the importance of Albee's contributions to bone surgery, notably transplantation for tuberculosis of the spine and inlay graft, both of which he has done so much to develop, this book has been looked forward to with considerable interest. These two subjects have received the brunt of the author's attention in this volume, both being very well presented and profusely illustrated. His own technique, which is so efficiently developed, is very clearly demonstrated and should be very helpful to those interested in bone surgery.

The treatment of fractures of the femur and fractures of the os calcis and patella with bone pegs is also a very distinct advance, and shows the development of the author's technique. The entire book is most valuable for those interested in bone surgery.

Localization by X-Rays and Stereoscopy. By SIR JAMES MACKENZIE DAVIDSON. Cloth, $3.00. (*New York: Paul B. Hoeber, 1916.*)

The author discusses the various methods employed in locating various bodies. He does not confine himself to the roentgenological methods, but includes others, for instance, those in which the telephone and electro-magnet are used.

The methods described, although somewhat complicated, are very exact and should be of great assistance, particularly in locating deep-seated bodies.

The chapter dealing with the exact localization of deep-seated bodies in the eye is most interesting and instructive. The technique is very accurate and consequently the results are uniformly good.

Throughout the book various ingenious techniques are given, which the author employs not only in the subject under discussion but also in his general roentgenological work.

The final chapter discusses protection for the roentgenologist. This is particularly opportune, since the great amount of localization that is being done incidental to the war is beginning to show some harmful effects upon the roentgenologists.

This book should be very valuable to all roentgenologists, but particularly to those who are operating in large industrial centers where the need of localization of foreign bodies is very great.

F. H. B.

Diagnosis and Treatment of Surgical Diseases of the Spinal Cord and Its Membranes. By CHARLES A. ELSBERG, M. D., F. A. C. S. Cloth, $5.00. (*Philadelphia and London: W. B. Saunders Company, 1916.*)

Treatises on surgery of the spinal cord are quite infrequent and for this reason this book is received with considerable interest and should be of much assistance. It is mainly a summary of the author's experiences. The technique of his operations and the general run of cases that he has encountered give one a very good idea of surgery and surgical conditions of the spinal cord. The part on tumors of the spinal cord is particularly good, especially from a pathological and operative standpoint. The subjects are well presented, although somewhat redundant. The illustrations are good.

A Text-Book of Physiology for Medical Students and Physicians. By WILLIAM H. HOWELL, PH. D., M. D., SC. D., LL. D., Baltimore, Md. Sixth edition, thoroughly revised. Cloth, $4.00 net. (*Philadelphia and London: W. B. Saunders Company, 1915.*)

The sixth edition of any text-book calls for but brief consideration in this place because its field of usefulness has been established. Howell's Physiology has maintained its preeminence for two chief reasons: First, because the author has retained a thoroughly modern point of view in dealing with the various phases of a now complex subject, as is indicated by his treatment of the newer literature; and second, because the style of presentation is simple and clear. An illustrated text-book of physiology which accomplishes these ends, and yet is held within a thousand octavo pages of ten-point type, is worthy of its success.

The Origin and Nature of the Emotions. By GEORGE W. CRILE, M. D. Cloth, $3.00. (*Philadelphia and London: W. B. Saunders Company, 1915.*)

In this volume eight addresses delivered by Dr. Crile before various societies during the past few years have been brought together. The titles of the addresses give a clue to their contents and are as follows: (1) Phylogenetic Association in Relation to Certain Medical Problems; (2) Phylogenetic Association in Relation to the Emotions; (3) Pain, Laughter and Crying; (4) The Relation Between the Physical State of the Brain-Cells and Brain Functions—Experimental and Clinical; (5) A Mechanistic View of Psychology; (6) A Mechanistic Theory of Disease; (7) The Kinetic System; (8) Alkalescence, Acidity, Anesthesia—a Theory of Anesthesia.

The author of these addresses has a fertile imagination and delights in attempting the formulation of general laws that epitomize the data slowly accumulated by clinical and pathological research. In the papers before us he attempts to correlate many of the known facts of surgical pathology and physiology with facts of general biology. Thus after discussing the phylogenetic origin of the emotions, for example, he tries to establish the pathological identity of surgical and emotional shocks. With the aid of laboratory associates, he supports his views based upon clinical observations with laboratory studies (histological, chemical, physiological).

In the experimental work, animals were subjected to fear and anger, to infection and to protein poisoning, and later the histological changes in the organs and tissues were studied. Crile describes certain alterations in the brain, the adrenals and the liver, that he believes are due to emotion, infection, or poisoning. Since the changes were limited to the three organs mentioned,

he groups these organs together into what he calls the "kinetic system" and suggests that no member of the system can act without the cooperation of the other two. The changes that the organs of the kinetic system undergo in the ordinary wear and tear of life are repaired largely, he believes, during sleep, a view which he also supports by experiments on animals.

Crile, in a pleasing way, draws upon the researches and hypotheses of Darwin, of Sherrington, and of Cannon, to interpret his clinical studies and his experimental observations. The book makes interesting reading and though conservative workers will probably withhold judgment regarding the interpretation of the histological findings and of the experiments pending further studies, still the book should be stimulating to thought and research and will be read by physicians, medical students and biologists with interest and pleasure. The illustrations add to the attractiveness of the several papers. L. F. B.

BOOKS RECEIVED.

Bacteriology, General, Pathological and Intestinal. By Arthur Isaac Kendall, B. S., Ph. D., Dr. P. H. Illustrated with 98 engravings and 9 plates. 1916. 8°. 651 pages. Lea & Febiger, Philadelphia and New York.

Stanford University Medical Publications. Bulletin No. 3, 1914-1915. 1915. 4°. San Francisco.

American Ophthalmological Society. Transactions of the American Ophthalmological Society. Fifty-second Annual Meeting, Washington, D. C. Vol. XIV, Part II. 1916. 8°. Philadelphia.

Carnegie Endowment for International Peace. Founded December 14, 1910. Year Book for 1916. 8°. 204 pages. Washington, D. C.

A Practical Treatise on Disorders of the Sexual Function in the Male and Female. By Max Hühner, M. D. 1916. 8°. 318 pages. F. A. Davis Company, Philadelphia; Stanley Phillips, London.

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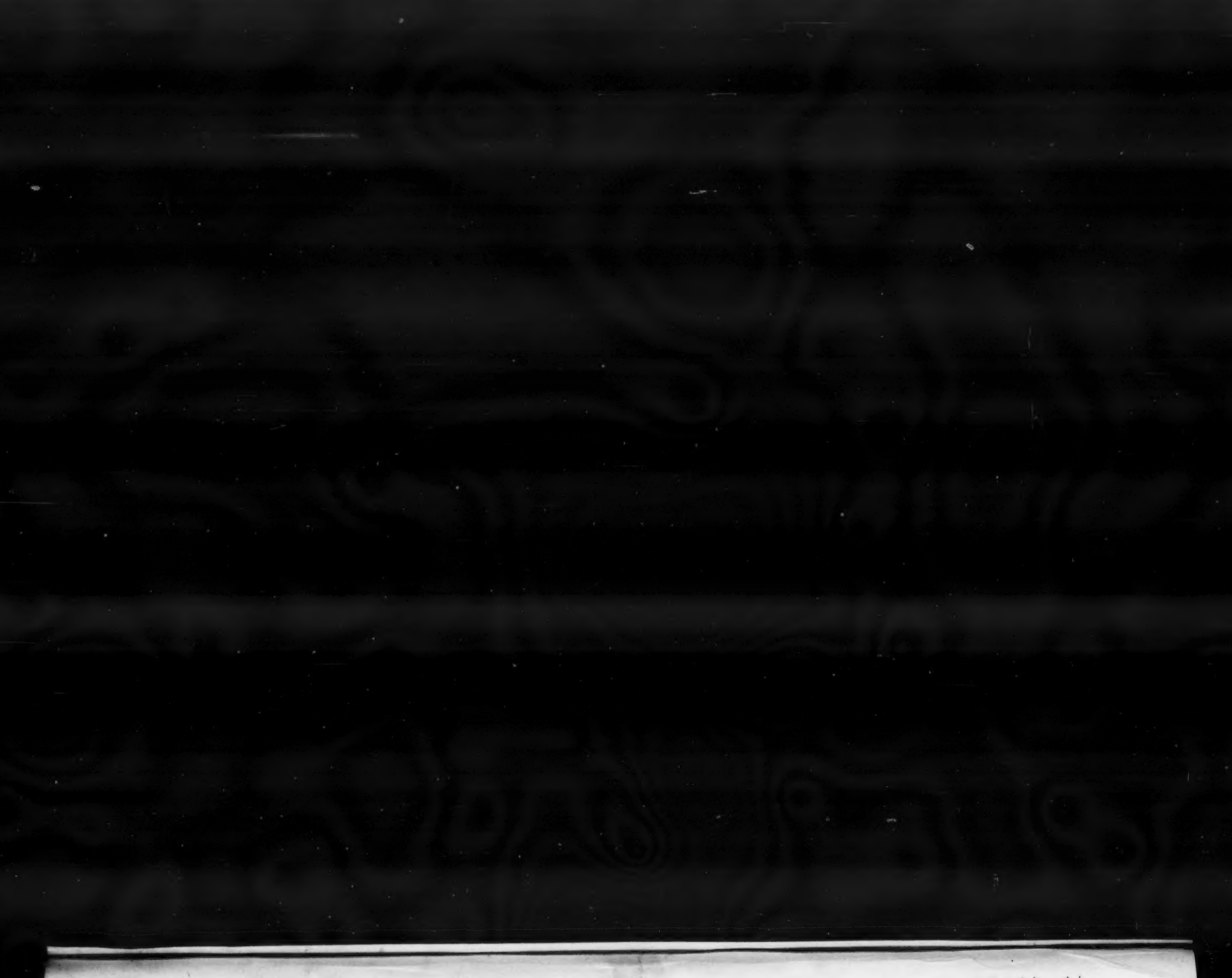
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